Université de Montréal

Development of New Methods for the Synthesis and Applications of Functionalized Trisubstituted Cyclopropanes and Bicyclo[1.1.0]butanes

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Development of New Methods for the Synthesis and Applications
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Résumé

De par ses propriétés uniques, le motif cyclopropane est largement répandu dans les composés bioactifs et d'intérêt pharmaceutique. Des efforts d'envergure ont été déployés pour accéder directement à des cyclopropanes substitués. La recherche présentée dans cette thèse décrit de nouvelles méthodes de préparation de cyclopropanes polysubstitués et leur application pour la synthèse de bicyclo[1.1.0]butanes.

Pour accéder à une variété de *cis*-iodocyclopropanes, une zinciocyclopropanation diastéréosélective a été développée en utilisant les réactifs hétéro-dihalocarbénoïdes récemment décrits par le groupe Charette. La procédure a été simplifiée, notamment en augmentant la concentration. L'utilisation de ces nouvelles conditions a permis d'élargir considérablement l'étendue et l'efficacité de la réaction.

Bien que leur synthèse soit difficile, les petits systèmes carbobicycliques rigides possède une réactivité unique en tant qu'intermédiaires pour des molécules complexes. Les iodocyclopropanes *cis* issus du premier projet ont été utilisés pour la synthèse de bicyclo[1.1.0]butanes riches en électrons et substitués aux positions 2-, 2,2- et 2,4. Comme la nature et la position des substituants est opposées à celles des bicyclo[1.1.0]butanes précédemment développés, ces composés peu étudiés jusqu'à maintenant, ont une réactivité intéressante.

À l'aide d'un précurseur de carbène diiodosilylméthylboronate, une *gem*-borosilylcyclopropanation organocatalysée et activée par la lumière visible a été développée et appliquée à de nombreux dérivés du styrène. Cette méthode a permis la préparation de borosilylcyclopropanes 1,1,2-tri- et 1,1,2,2-tétrasubstitués avec un excellent contrôle diastéréosélectif. Différentes réactions de post-fonctionnalisation soulignent la versatilité de cette nouvelle entité.

En complément, une *gem*-borosilylcyclopropanation rapide et efficace médiée par micro-ondes sans catalyseur a été développée. Cette méthode est une alternative aux conditions développées en photochimie.

Mots clés : Cyclopropane, carbénoïde, Simmons-Smith, iodocyclopropane, bicyclo[1.1.0]butane, catalyse photorédox, photochimie, *gem*-borocyclopropylsilane.

Abstract

The cyclopropane moiety is prevalent in bioactive compounds and drug candidates due to its unique properties. Extensive effort has been made to develop straightforward access towards highly substituted cyclopropanes. The research presented in the thesis describes new methods for polysubstituted cyclopropanes and their application in the preparation of bicyclo[1.1.0]butanes.

To access a variety of *cis*-iodocyclopropanes, a diastereoselective zincocyclopropanation using modified conditions was developed by applying hetero-dihalocarbenoids recently reported by the Charette group. The procedure increased the reaction concentration, streamlined the process, and improved the efficiency of the reaction. The substrate scope was significantly expanded using the newly developed conditions.

Strained small carbobicyclic systems are valuable synthons for complex molecules despite their challenging synthesis. The *cis*-iodocyclopropanes resulting from the first project were applied in the synthesis of electron-rich 2–, 2,2– and 2,4–substituted bicyclo[1.1.0]butanes. Since the nature and the position of the substituents were opposite compared to previously developed bicyclo[1.1.0]butanes, the underexplored scaffolds exhibited different reactivity.

The organocatalyzed visible-light mediated *gem*-borosilylcyclopropanation of styrene derivatives was developed using a diiodosilylmethylboronate carbene precursor. The method enabled the preparation of 1,1,2-tri– and 1,1,2,2–tetrasubstituted borosilylcyclopropanes with excellent diastereocontrol. Post-functionalization reactions highlighted the synthetic versatility of the novel entities.

A catalyst-free microwave-assisted time-efficient *gem*-borosilylcyclopropanation reaction was complementary developed, offering an alternative to photochemistry.

Keywords: Cyclopropane, carbenoid, Simmons-Smith, iodocyclopropane, bicyclo[1.1.0]butane, photoredox catalysis, photochemistry, *gem*-borocyclopropyl silane.

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List of Schemes

List of Abbreviations

4CzIPN	2,4,5,6-Tetrakis(9H-carbazol-9-yl)isophthalonitrile
Å	Angstrom
abs	Absorbance
Ac	Acetate
Ad	Adamantyl
AIBN	Azobisisobutyronitrile
Ak	Alkyl
ALK	Anaplastic lymphoma kinase
aq	Aqueous
Ar	Aromatic
BCB	Bicyclo[1.1.0]butane
BCH	Bicyclo[2.1.1]hexane
BCP	Bicyclo[1.1.1]pentane
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Boc	*tert*-Butyloxycarbonyl
BMS	Bristol-Myers Squibb
Bn	Benzyl
br	Broad
BTPCP	4-Bromophenyl-2,2-diphenylcyclopropanecarboxylate
Bu	Butyl
Bz	Benzoyl
C	Celsius
CAN	Ceric ammonium nitrate
cat	Catalytic
CFL	Compact fluorescent lamp
COD	1,5-Cyclooctadiene
Cys	Cysteine
δ	Chemical shift
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dan	1,8-Diaminonaphthalene
DBL	Dioxaborolane
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density functional theory
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide

DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
E	Electrophile
EDG	Electron donating group
ee	Enantiomeric excess
Et	Ethyl
EY	Eosin Y
equiv	Equivalent
ESI	Electrospray ionisation mass spectrometry
EWG	Electron withdrawing group
FDA	Food and Drug Administration
FG	Functional group
g	Gram
gem	*geminal*
h	Hour
hex	Hexyl
HIV	Human immunodeficiency virus
HOMO	Highest occupied molecular orbital
HRMS	High-resolution mass spectrometry
hν	Light irradiation
i	iso
ISC	Intersystem crossing
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
J	Joule
J	Coupling constant
k	Rate
kg	Kilogram
λ	Wavelength
λ_{max}	Maximal absorption wavelength
L	Ligand
LED	Light-emitting diode
LG	Leaving group
LUMO	Lowest unoccupied molecular orbital
m/z	Mass on charge ratio
m	Meter
m	Multiplet
m	*meta*
M	Molar
Me	Methyl
Mes	Mesityl
MHz	Megahertz
µL	Microliter
MIB	(Morpholino)isoborneol
MIDA	Methyliminodiacetic acid
min	Minute

MIRC	Michael initiated ring closure
mL	Milliliter
mmol	Millimole
mol	Mole
mg	Milligram
MS	Mass spectrometry
Ms	Methanesulfonyl
n	*normal*
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
nm	Nanometer
NMR	Nuclear magnetic resonance
NTTL	*N*-1,2-Naphthaloyl-*tert*-leucine
Nu	Nucleophile
o	*ortho*
p	*para*
Ph	Phenyl
Phen	Phenanthroline
pin	Pinacolato
piv	Pivalate
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
pK_a	Acid dissociation constant at logarithmic scale
PPTS	Pyridinium *para*-toluenesulfonate
Pr	Propyl
q	Quartet
RRCK	Ralph Russ canine kidney
RSE	Ring strain energy
rt	Room temperature
s	Second
s	Singlet
SCE	Saturated calomel electrode
SET	Single-electron transfer
SFC	Supercritical fluid chromatography
t	Time
t	*tert*
TAD	1,2,4-Triazole-3,5-dione
TBAB	*n*-Tetrabutylammonium bromide
TBAF	*n*-Tetrabutylammonium fluoride
TBAT	*n*-Tetrabutylammonium difluorotriphenylsilicate
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
Tf	Triflate
TFAA	Trifluoroacetic acid anhydride

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N'N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
t_R	Residence time
UV	Ultraviolet
vis	Visible
vs	*versus*
W	Watt
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

To my family,

In the middle of every difficulty lies opportunity

- *Albert Einstein*

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1. Introduction

1.1 Introduction to Cyclopropanes

The three-membered ring, being the smallest carbocycle possible, has a rigid geometrical framework which contributes to spatially distinct well-defined substituents and atypical C–C bond angles of 60°.[1] Because of the specific characteristics, not only is the cyclopropane entity a potential alkene or *gem*-dimethyl bioisostere, but it can also add rigidity to a compound's general structure.[2] Therefore, the moiety ranks among one of the most targeted units found in drug candidates.[3] In addition to the prevalence of the structural motif in biologically active compounds,[4] the cyclopropane ring was present in eight of the 200 best-selling therapeutic agents approved by the American Food and Drug Administration (FDA) in 2021 and in 166 drug candidates in various clinical trials as of 2015.[5] As a result, the development of a broad toolbox for the efficient formation of cyclopropane derivatives has been a significant focus in chemical research over the past century.[6] The syntheses of cyclopropane cores as well as their functionalization will be discussed in the thesis. The following section highlights important biologically active trisubstituted cyclopropanes from natural products or potential drug candidates.

1.1.1 Importance and Applications of Trisubstituted Cyclopropanes

A selection of biologically active compounds incorporating 1,2,3- and 1,1,2-trisubstituted cyclopropanes are presented below (Figures 1.1 and 1.2). 1,2,3-Trisubstituted cyclopropanes **1.1a-d** were specifically targeted and recently designed as herpes simplex type I and varicella-zoster antivirals, since cyclopropane nucleosides were known as antiviral candidates (Figure 1.1).[7] Another 1,2,3-trisubstituted cyclopropane was found in the antifungal agent (+)-ambruticin **1.2**, which was isolated from myxobacterium *Polyangium cellulosum*.[8] The natural product was found to be selectively effective against 14 different fungal strains, but inactive against gram-positive or gram-negative bacteria. Another subcategory of 1,2,3-trisubstituted cyclopropanes is the bicyclo[1.*n*.0]alkanes. For example, bicyclo[1.1.0]butane (BCB) fatty acid **1.3** was surprisingly isolated from the hemoprotein-lipoxygenase fusion protein from the cyanobacterium *Anabaena* PCC 7120.[9] The compound is the only known bioactive molecule containing a BCB core isolated from a natural source so far.

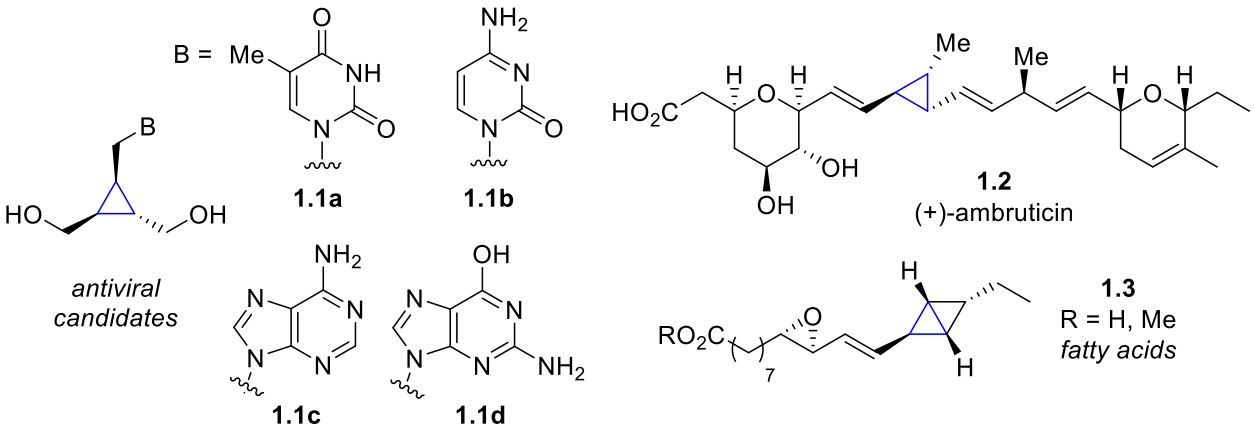


Figure 1.1 Examples of 1,2,3-trisubstituted cyclopropanes of interest.

1,1,2-Trisubstituted cyclopropanes were found in natural products and bioactive synthetic molecules as well (Figure 1.2). For instance, cyclopropane **1.4** was recently synthesized as an inhibitor of the anaplastic lymphoma kinase (ALK), which was involved in cancer treatment.[10] Incorporating a cyclopropane restrained the mobility of the chain and anchored the backbone and the conformation of the structure, while maintaining a small structure compared to larger rings analogs. Milnacipran **1.5**, commercially known as Ixel®, was approved for the treatment of depressive disorders, anxiety, epilepsy, and strokes.[11] Lastly, both bicifadine **1.6a** and DOV21947 **1.6b** block the serotonin and norepinephrine reuptake transporters and were evaluated for the treatment of pain and other diseases related to the neurotransmitters' transporters.[12] Hence, development of trisubstituted cyclopropanes are attractive building blocks, and methods to access them are in demand.

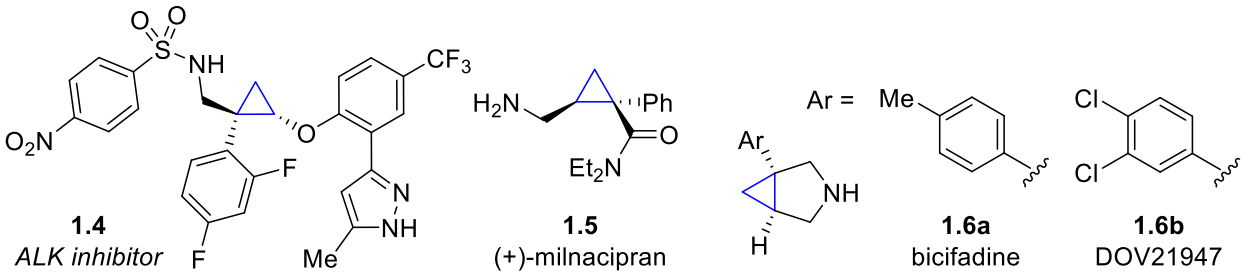


Figure 1.2 Examples of biologically active 1,1,2-trisubstituted cyclopropanes.

1.1.2 Functionalized Cyclopropanes in Synthetic Organic Chemistry

Among the different strategies to incorporate a three-membered moiety into complex molecules, the most efficient one is the use of functionalized cyclopropanes, such as iodo-, boro- and silyl-cyclopropanes (Figure 1.3).[13]

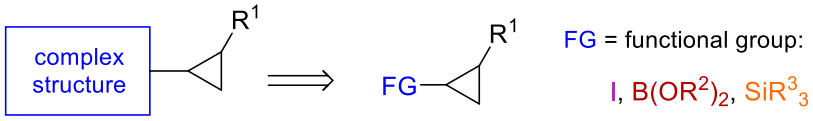
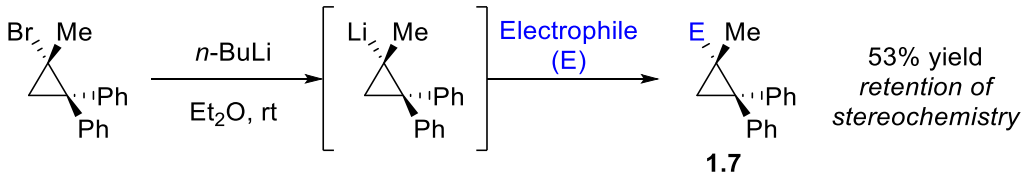


Figure 1.3 Functionalized cyclopropanes as retrosynthetic strategy to add cyclopropanes to a complex structure.

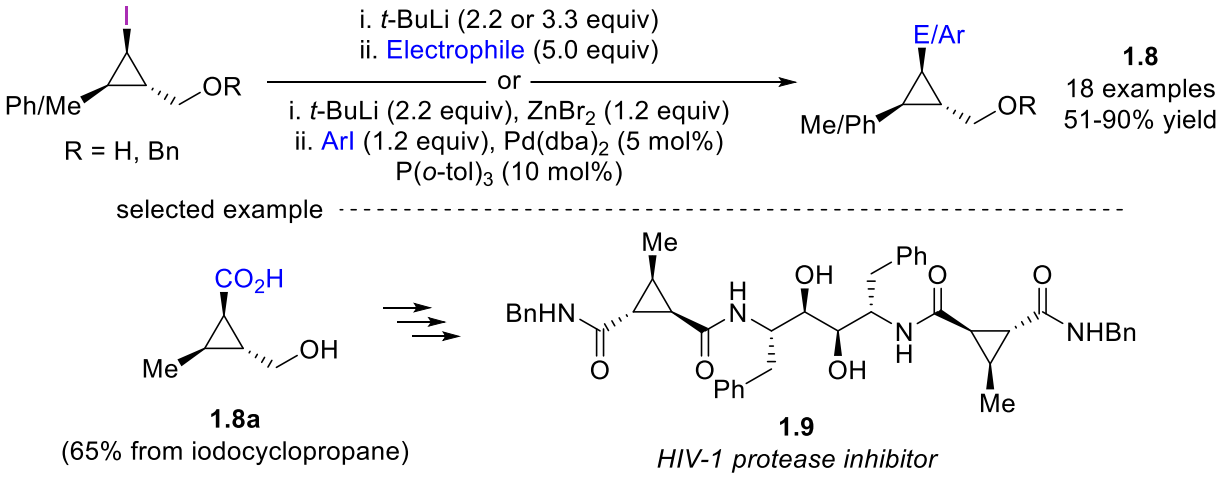
1.1.2.1 Bromo- and Iodo-cyclopropanes in Total Synthesis

Due to the relatively weak strength of the C–Br and C–I bonds, bromo- and iodo-cyclobutanes are convenient synthons for the preparation of functionalized cyclopropanes. Halocyclopropanes can be used for the *in situ* generation of cyclopropyl-lithium compounds via halogen-lithium exchange (Scheme 1.1). The first reported cyclopropyl lithium species was obtained starting from a bromocyclopropane. The incorporation of electrophiles on cyclopropyl lithium demonstrated retention of configuration (**1.7**).[14]



Scheme 1.1 Cyclopropyl-lithium intermediate to incorporate an electrophile to cyclopropane with retention of stereochemistry.

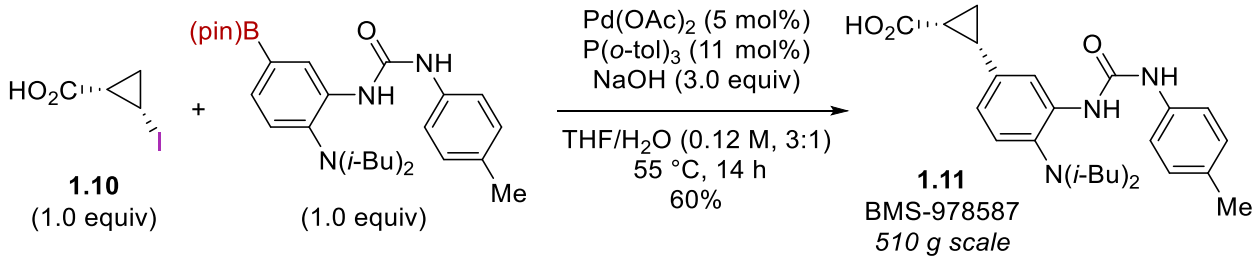
In 2012, cyclopropyl lithium compounds were reported and were used as nucleophiles or as intermediates in Negishi cross-couplings (Scheme 1.2).[15] Among the 18 examples of 1,2,3-trisubstituted cyclopropanes **1.8** generated, cyclopropylcarboxylic acid **1.8a** was further functionalized for the formal synthesis of a biologically active peptidomimetic molecule **1.9**. Cyclopropyl lithium compounds were also used in the synthesis of BCB **1.3** (Figure 1.1), which will be further discussed in section 3.1.2.



Scheme 1.2 Synthesis of 1,2,3-trisubstituted cyclopropanes from iodocyclopropanes and the formal synthesis of an HIV-1 protease inhibitor using cyclopropylcarboxylic acid **1.8a**

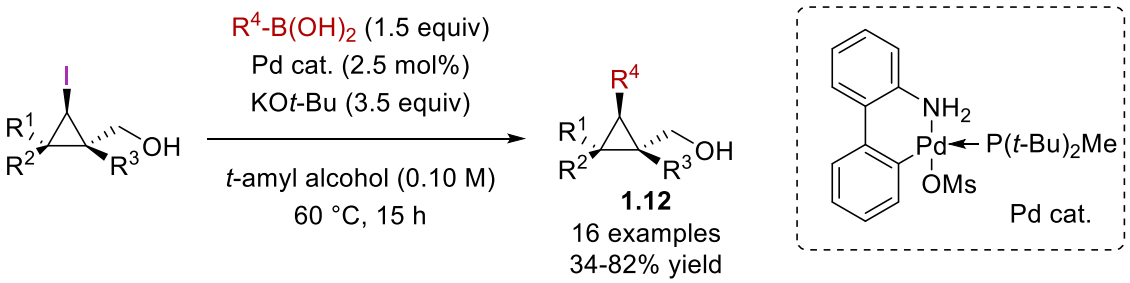
As various functional groups in cyclopropane-containing natural products were not compatible with reactive organolithium intermediates, more versatile and mild conditions were required for functionalization. As such, iodocyclopropanes were employed in cross-coupling as an electrophilic partner.

The commercially available iodocyclopropanecarboxylic acid **1.10**, being incompatible with basic organometallic species due to the carboxylic acid group, was involved in the last step of the 510 g scale synthesis of BMS-978587 **1.11** (Scheme 1.3).[16] The potential drug candidate was discovered and developed by Bristol-Myers Squibb as a potent small molecule inhibitor of indoleamine-2,3-dioxygenase, which is an enzyme involved in the proliferation of tumors. Its overexpression was involved in a wide range of human cancers and its inhibition was shown to reinvigorate the natural immune response to cancer cells.[17] To support the development of the potential drug candidate, a rapid, safe, and robust synthesis allowing for its large-scale production was required.[16] Iodocyclopropane was coupled with an arylboronic ester in a Suzuki-Miyaura cross-coupling in a 60% yield.



Scheme 1.3 Hecto-scale Suzuki-Miyaura cross-coupling on iodocyclopropanecarboxylic acid.

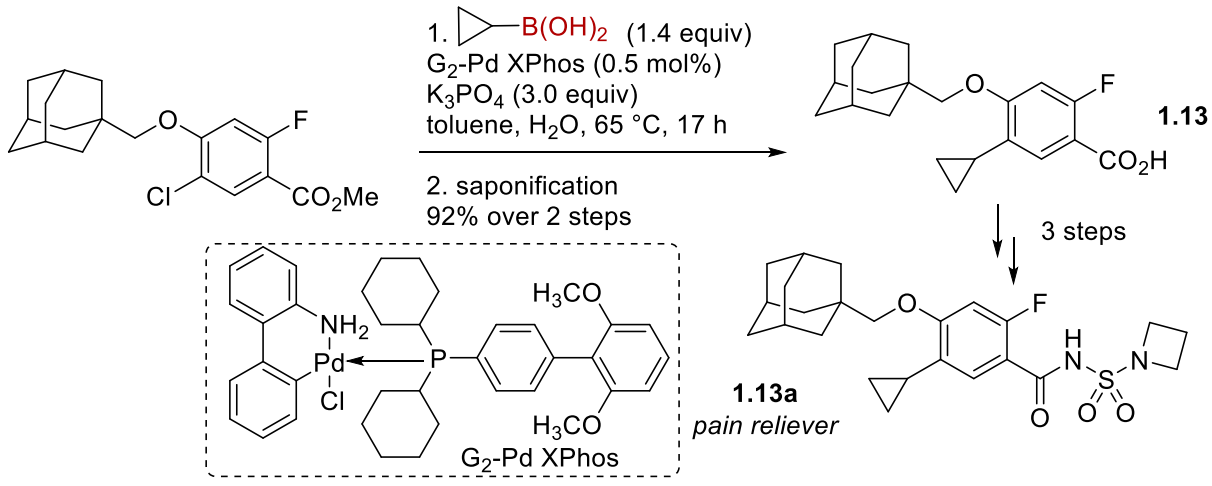
The application of iodocyclopropanes in Suzuki-Miyaura cross-couplings was demonstrated by Dr. Emmanuelle Allouche, a former Ph.D. Charette group member (Scheme 1.4).[18] The development of the new conditions allowed access to 1,2,3-trisubstituted cyclopropylmethanols **1.12**.



Scheme 1.4 Suzuki-Miyaura cross-coupling conditions developed by Allouche.

1.1.2.2 Synthetic Utility of Borocyclopropanes

Other functional groups used to incorporate a three-membered ring moiety into complex molecules include boronic acids or esters. Versatile borocyclopropanes can be employed as the nucleophilic partners in the Suzuki-Miyaura cross-coupling. For example, the commercially available cyclopropylboronic acid was involved in the total synthesis of an inhibitor of a voltage-gated sodium channel expressed in pain-sensing nerve C-fibers **1.13a** and thus a valuable drug discovery target involved in pain treatment (Scheme 1.5).[19] Upon Suzuki-Miyaura cross-coupling with an aryl chloride, saponification, and recrystallization, the cyclopropane containing coupled adduct **1.13** was isolated in a 92% yield on a 7-kg scale.[20]



Scheme 1.5 Cyclopropyboronic acid as a building block in the synthesis of a pain relief medicine.

As organoborons are generally non-toxic and chemically and configurationally stable, they are convenient to use in the synthesis of cyclopropanes (Figure 1.3).[13] In addition to the previously mentioned Suzuki-Miyaura cross-coupling,[21] borocyclopropanes can participate in the Zweifel olefination, another type of cross-coupling allowing for stereoselective synthesis of alkenes through iodination of vinyl boronate complexes.[22] Cross coupling of organoborons with a heteroatom-containing coupling partners (nitrogen, oxygen or sulfur) can be achieved using the Chan-Lam-Evans coupling.[23] To prepare cyclopropylamines or cyclopropanols, amination[24] or oxidation[25] can be performed on borocyclopropanes. Lastly, the Matteson homologation can be used with cyclopropylboronates, allowing for the addition of a functionalized carbon between the cyclopropane and the boronate group.[26]

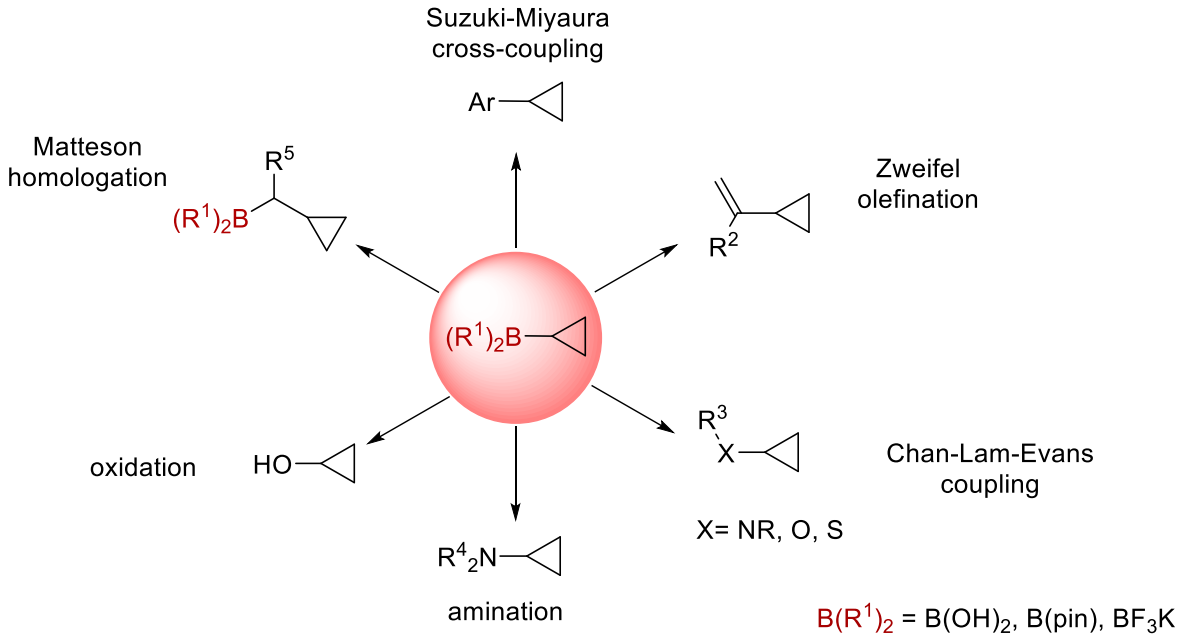


Figure 1.4 Synthetic utility of borocyclopropanes.

1.1.2.3 Silylcyclopropanes as Synthetically Useful Intermediates

Silanes are well known for their use as protecting groups due to their stability under various reaction conditions.[27] Although organosilanes are usually less reactive than organoborons, they can be synthetically useful under the appropriate reaction conditions.[27] Similar to boronates, the reactivity of silanes depends on the nature of their substituents. As such, alkoxysilanes or

fluorosilanes are more reactive than alkylsilanes. To increase alkylsilane reactivity, a fluorine activator, such as cesium fluoride and tetra-*n*-butylammonium fluoride (TBAF), can be added to form a pentavalent silane, which is more reactive than the corresponding tetravalent species. Cyclopropylsilanes can undergo some of the transformations of common silanes (Figure 1.4).[27] Similar to organoborons, organosilanes can participate in cross-couplings for C–C bond formation, specifically in the Hiyama-Denmark cross-coupling.[28] Cyclopropylsilanes can be directly oxidized to cyclopropanol via the Kumada-Fleming-Tamao oxidation with the addition of fluorinated reagents.[29] Desilylative electrophilic condensation with aldehydes as the electrophiles is possible on cyclopropylsilanes using a fluorinated activator.[30]

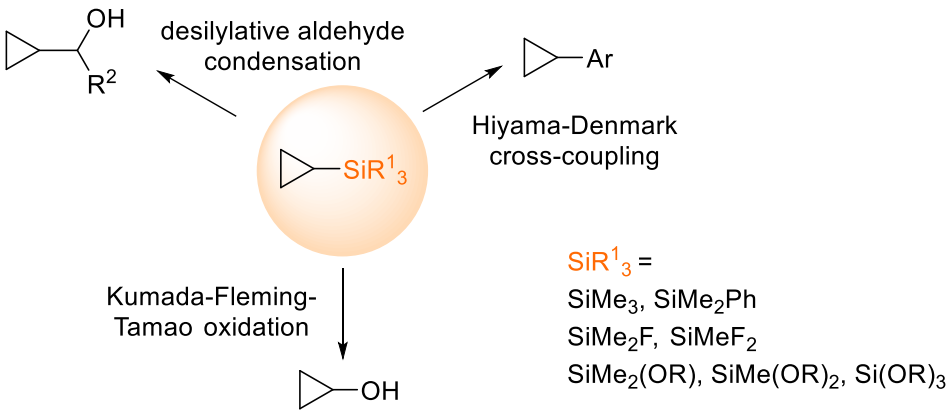


Figure 1.5 Transformation of cyclopropylsilanes.

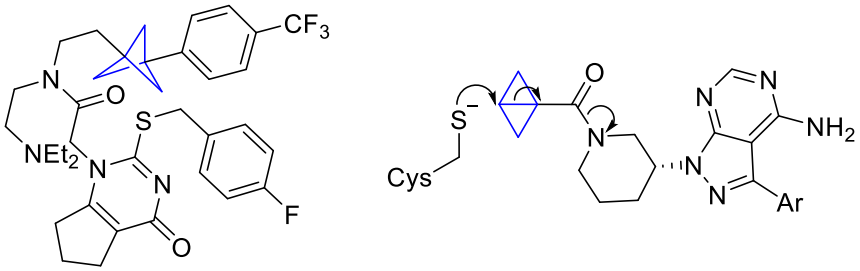
1.2 Introduction to Bicyclo[1.1.0]butanes

1.2.1 Small Strained Ring Systems in Medicinal Chemistry

Medicinal chemists are routinely turning to rigid motifs and unexplored chemical space to improve the pharmacokinetic properties of drug candidates. The organic chemistry research involved is one of the rate-limiting factors in drug discovery.[31] For example, the benzene ring was ranked as the most frequently used ring in drug candidates.[3] Replacement of the ring by a saturated functional group was found to improve physical, chemical or biochemical properties. The replacement is one way to prevent π-stacking.[32] Aromatic rings were replaced by small strained ring systems in therapeutic agents in the examples *vide infra* (Figure 1.6). Through a challenging synthesis, the *p*-substituted phenyl ring in darapladib, which was targeted for the treatment of atherosclerosis,[33] was replaced with bicyclo[1.1.1]pentane (BCP) **1.14**. The drug-target binding

mode was confirmed by X-ray crystallography and was similar to that of the parent compound. Improved pharmacodynamic properties were observed, such as membrane permeability, aqueous solubility, and low clearance as compared to its parent drug.

A recent study showed that strained electron-poor bicyclo[1.1.0]butane (BCB) amides, such as **1.15**, could act chemoselectively as an electrophile with cysteine thiol residues.[34] The features of BCB amides were leveraged as a new protein bioconjugation tool. Irreversible protein modification was completed using BCB amides as latent electrophiles, for instance using chemoselectively a cysteine residue on BCB-ibrutinib (**1.15**). The reactivity profile of the BCB amide was successfully exploited for the development of a covalent inhibitor, with higher target selectivity in the development of lymphocytes (for immunology purposes) as compared to the corresponding previous probe. In most previously published replacements of benzenes, the bridgehead 1,3-substitution of the bicycle mimicked *p*-substituted arenes.[35]



1.14
BCP-darapladib

1.15
BCB-ibrutinib

Figure 1.6 Structure of bicyclo[1.1.1]pentane-darapladip and bicyclo[1.1.0]pentane-ibrutinib.

1.2.1.1 Previous Work on *ortho*– and *meta*-Substituted Benzene Isosteres

The desire to replace *o*– and *m*-functionalized aromatics with saturated scaffolds in bioactive molecules is undeniably due to the lack of synthetic methods, rather than the lack of desire to achieve the 2-functionalization in bicyclic cores, which was numerously mentioned over the years.[32] Only a few examples of *o*– and *m*-substituted aromatic isosteres have been published up to now. Baran reported a divergent synthesis to reach various synthetic fragments to incorporate analogous 1,2-disubstituted bicyclo[1.1.1]pentane (1,2-BCP) as *m*-analog in commercial drugs and to test them against their corresponding target.[36] Along with *p*-arene bioisosteres, 1,2-BCPs overall emerged as equipotent inhibitors but the added level of three-dimensionality had a positive effect on the drugs' aqueous solubility and passive permeability. For instance, the membrane-

permeability of anti-cancer agent sonigedib **1.16a** was improved by a 50-fold in **1.16b** when the *m*-substituted arene core ring was replaced by 1,2-BCP in **1.16b** (Figure 1.7).

When replacing aromatic rings with bicyclic isosteres in druglike compounds, chirality adds a new synthetic challenge. In Baran's work, BCP enantiomers were separated using supercritical fluid chromatography (SFC).[36] The challenge of enantioselective synthesis associated with complex bicyclic moieties are worth overcoming due to their beneficial effects on drug-target specific binding.

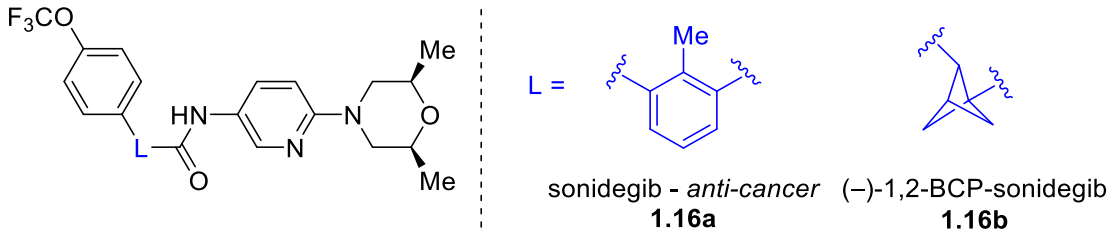


Figure 1.7 Structures of sonidegib and (−)-1,2-bicyclo[1.1.1]pentyl-sonidegib.

Due to the synthetic challenges associated with their syntheses, up to now, only one type of saturated bioisostere was specifically designed to mimic *o*-substituted benzenes. 1,2-Disubstituted bicyclo[2.1.1]hexanes (BCH) **1.17b** and **1.18b** were synthesized and tested against the corresponding *o*-substituted benzene analogs, namely the antihypertensive drug valsartan **1.17a** and the fungicide boscalid **1.18a** (Figure 1.8).[37] The comparison in crystallographic analyses of the compound bound to the protein target revealed high similarity in drug-target binding in both scaffolds. Replacing the benzene fragment core in model compounds increased their water solubility.

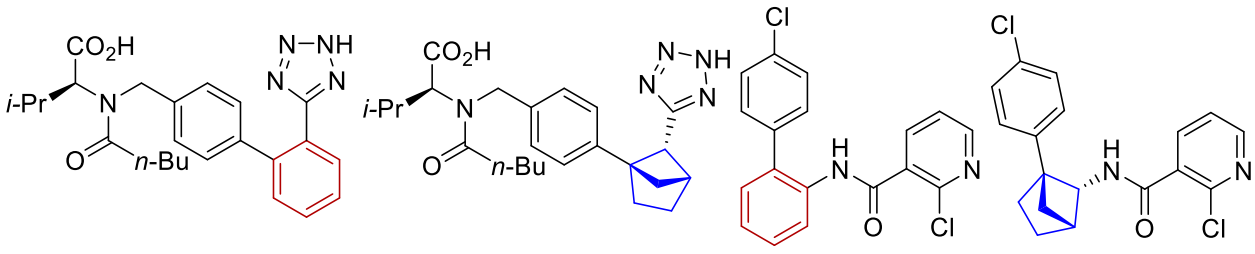


Figure 1.8 Bicyclo[2.1.1]hexanes as *o*-substituted bioisosteres aromatics.

1.2.2 Importance of Bicyclo[1.1.0]butanes

The synthesis and reactivity of small, strained ring systems have been a fascination in organic chemistry for decades.[38] Strain-release reagents are defined as bi- or tricyclic molecules having over 50 kcal/mol strain energy that react via cleavage of their bridging bond resulting in the release of strain. The compounds are commonly designated as "spring-loaded" reagents.[38-40] Due to a lack of methods to access functionalized BCBs, the motifs are scarcely found in pharmaceuticals (Figures 1.6-1.8). The fully saturated bicyclo[1.1.0]butane, featuring a bridging C(1)–C(3) bond, is the smallest carbobicycle possible. Bond lengths and angles in BCB are distorted compared to typical sp^3-hybridized carbons by its structural bonding and its two rings at a 120° angle (Figure 1.9).[39] The ring strain energy (RSE) contained in BCB was calculated to be 66 kcal/mol.[40] Its high RSE, which arises from the destabilizing C(1)–C(3) interaction, makes its synthesis difficult and it is the source of its interesting "spring-loaded" reactivity. As a comparison, the cyclopropane ring, having 29 kcal/mol RSE, bears less than half the RSE contained in BCB. The addition of a substituent on BCB position 1 notably increases its stability by decreasing its RSE by 7 kcal/mol. Nevertheless, the bridge-head positions remained unsubstituted in the only natural BCB (Figure 1.1, **1.3**).

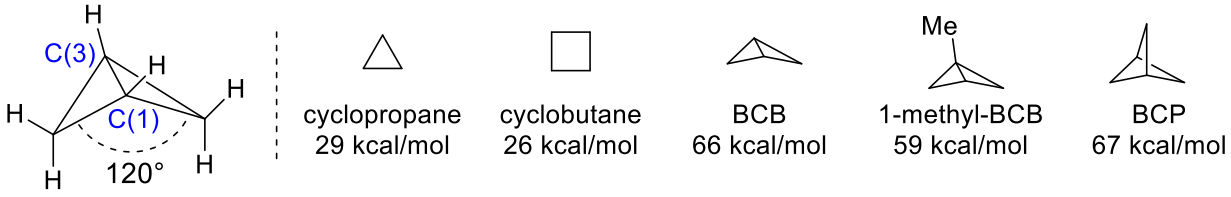


Figure 1.9 BCB structural shape and ring strain energy in small ring systems.

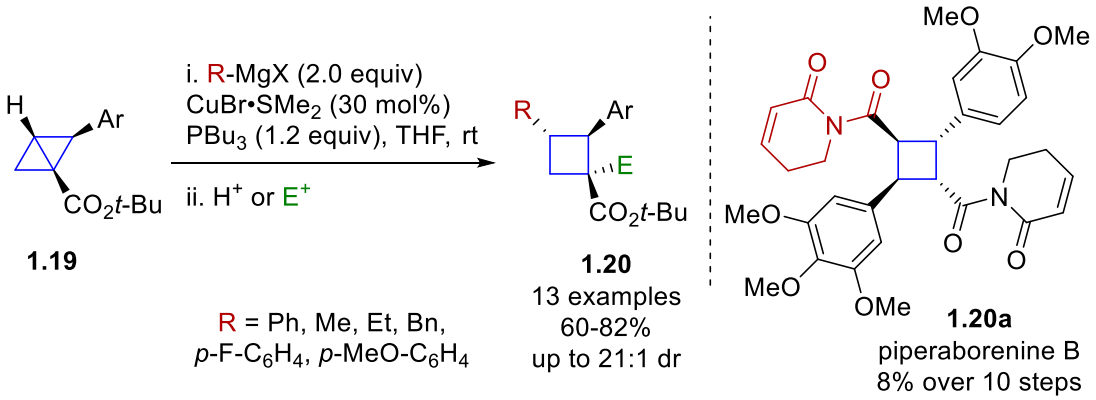
1.2.3 Synthetic Applications of Bicyclo[1.1.0]butanes

Functionalization of BCBs has gained attention in the past decade as the development of gram-scale syntheses of electron poor BCBs allowed the fruitful exploration of their distinct reactivity.[41] For discussion, selected applications of BCBs will be divided into 3 categories: nucleophilic and radical additions, cycloaddition reactions, and electrophilic additions.

1.2.3.1 Nucleophilic and Radical Additions

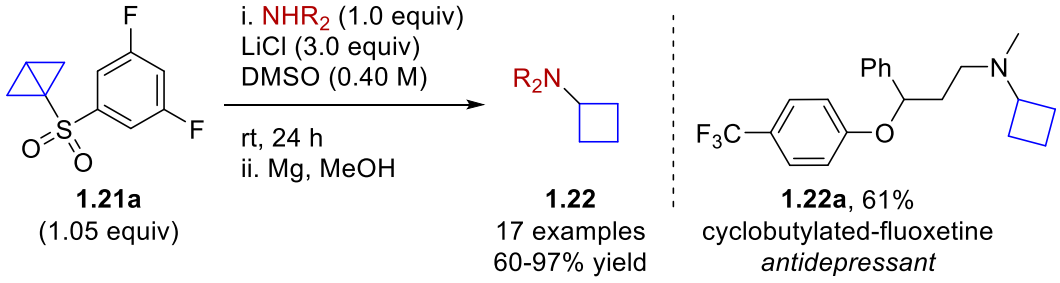
The most common functionalization of BCB is via ring strain release by the attack of a nucleophile. For instance, the ring-opening reaction by addition of a Grignard reagent on a BCB

1.19 was developed by Fox (Scheme 1.6).[42] In a one-pot process, following addition of the nucleophile, the resulting carbanion was quenched either by an acid or an electrophile (E). Directed by the substituents on the starting material, the resulting cyclobutanes **1.20** were obtained in high diastereoselectivity. The method was applied in the total synthesis of the natural product piperaborenine B **1.20a**, which was achieved in 8% overall yield in 10 steps.[43] The synthesis of BCB **1.19** will be discussed in chapter 3 (Section 3.1.3).



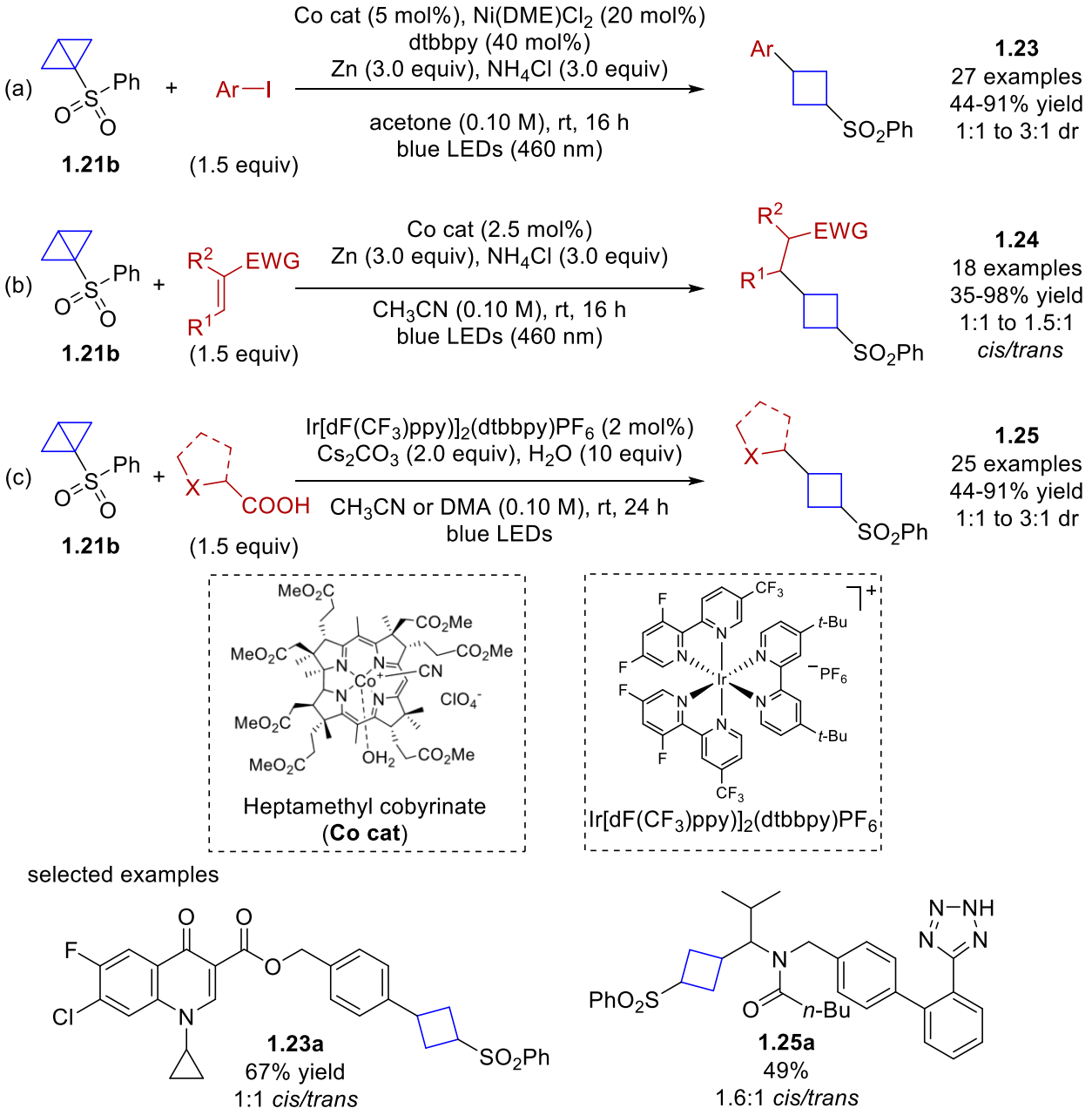
Scheme 1.6 Grignard addition to a BCB intermediate generates valuable cyclobutanes.

After developing a gram-scale synthesis of 1-((3,5-difluorophenyl)-sulfonyl)bicyclo[1.1.0] butane **1.21a**, Baran explored its nucleophilic ring-opening reactivity using a broad range of amines (Scheme 1.7).[44] The subsequent cleavage of the sulfone group afforded cyclobutylamines **1.22**. The method was applied to the late-stage functionalization of approved drugs, to provide for instance a cyclobutylated-fluoxetine **1.22a** in 61% yield. Since then, a variety of nucleophiles have been added to the BCB and its derivatives, as the sulfone electron-withdrawing group facilitates addition via stabilization of anionic intermediates.[45]



Scheme 1.7 Amine addition to a sulfonylated BCB.

Phenylsulfonyl BCBs were further explored in radical additions.[46] For example, BCB **1.21b** underwent a cobalt/nickel-catalyzed radical cross-coupling with aryl halides to provide 1-aryl-3-sulfone-cyclobutanes **1.20** in good to excellent yields (Scheme 1.8a).[47] The same cobalt catalyst, heptamethyl cobyrinate, enabled a radical addition to electron-poor alkenes without a nickel catalyst to give 1,3-disubstituted cyclobutanes **1.21** (Scheme 1.8b). Photochemically generated radicals also participated in strain release-motivated additions to furnish cyclobutanes **1.22** (Scheme 1.8c).[48] The radical addition methods were applied in the late-stage functionalization of fluoroquinolic acid derivative **1.20a** and valsartan **1.16a** (Scheme 1.8, bottom). In the aforementioned radical addition processes, the diastereoselectivity was dictated by the steric hindrance of neighboring substituents during the reaction of the electrophile with the cyclobutyl radical.[46] Compared to nucleophilic additions, radical additions apply to a wider scope of BCBs, as long as substituents are electron-withdrawing enough to stabilize the anion intermediate, which succeeds the cyclobutyl radical in the mechansim.[46]

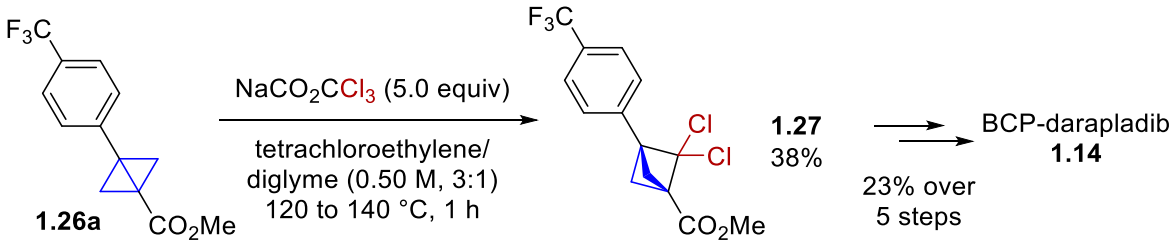


Scheme 1.8 Radical addition to arylsulfonyl BCBs.

1.2.3.2 Cycloaddition reactions of BCBs

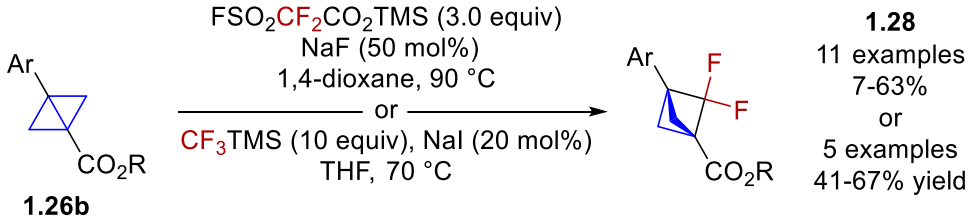
Since two carbons are involved in the ring strain release of BCBs, cycloaddition reactions have been explored. Two types of cycloadditions with BCB have been reported, namely [2+1] and [2+2] cycloadditions affording bicyclo[1.1.1]pentane (BCP) and bicyclo[2.1.1]hexanes (BCH) respectively. The [2+1] cycloaddition of a dichlorocarbene to a BCB was first reported in 1982.[49] The conditions were applied to methyl-BCB ester **1.26a** to provide dichloro-BCP **1.27** in a 38%

yield (Scheme 1.9).[33] Bioactive BCP-darapladib **1.14** (Figure 1.6) was obtained in 23% yield over 5 steps from BCP **1.27** (Scheme 1.9).



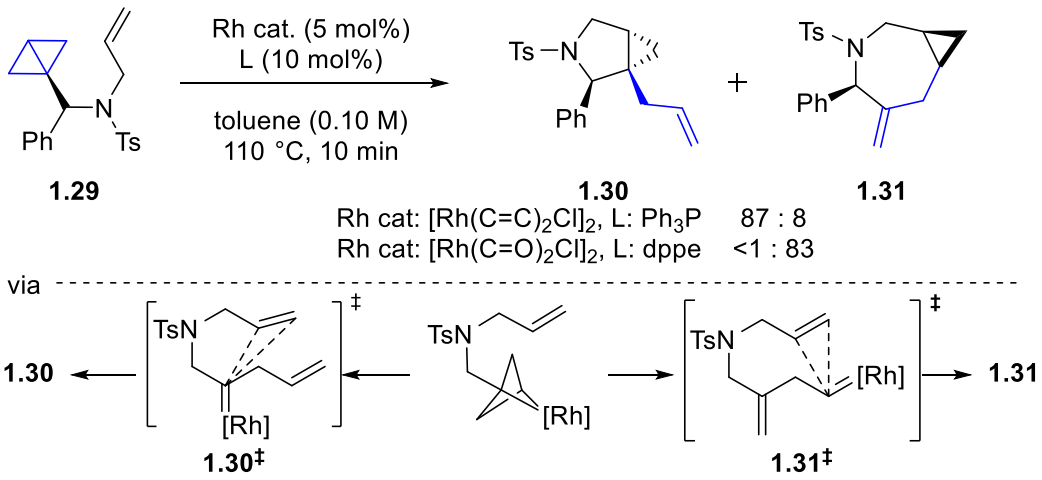
Scheme 1.9 Dichlorocarbene addition to a BCB.

Inspired by the cycloaddition with dichlorocarbene, two methods for the synthesis of difluoro-BCP **1.28** from BCB **1.26b** were reported almost simultaneously (Scheme 1.10).[50,51] Unfortunately, low to moderate yields were obtained using the methods and had poor functional group tolerance.



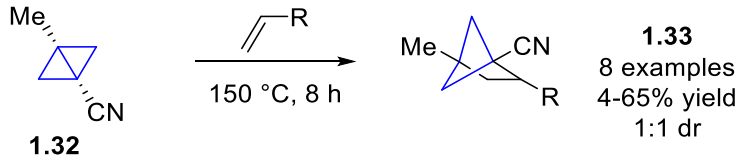
Scheme 1.10 Difluorocarbene addition to a BCB.

A [2+1] cycloaddition of BCB **1.29** could be performed via rhodium insertion in the central bond of *N*-allylated bicyclo[1.1.0]butylalkylamine. The resulting pyrrolidine **1.30** and azepane **1.31** were prepared with high levels of stereo- and regiocontrol and in good yields (Scheme 1.11).[52] A proposed mechanism suggested rhodium insertion to the BCB's bridged C–C bond. The resulting rhodium-containing BCP undergoes ring-opening and leads to an internal or external rhodium-metal carbene depending on the catalytic system. The least hindered catalyst provided the internal rhodium metal carbene **1.30‡**, then cyclopropanation with the *N*-allyl group provided pyrrolidine **1.30** (Scheme 1.11, bottom). Conversely, the most hindered catalytic system supplied an external metal rhodium carbene **1.31‡** to obtain azepane **1.31** upon cyclopropanation. A corresponding oxo-BCB allylic ether derivative provided a substituted furan and oxepane albeit with lower selectivity. The conditions were specific to the two substrates.



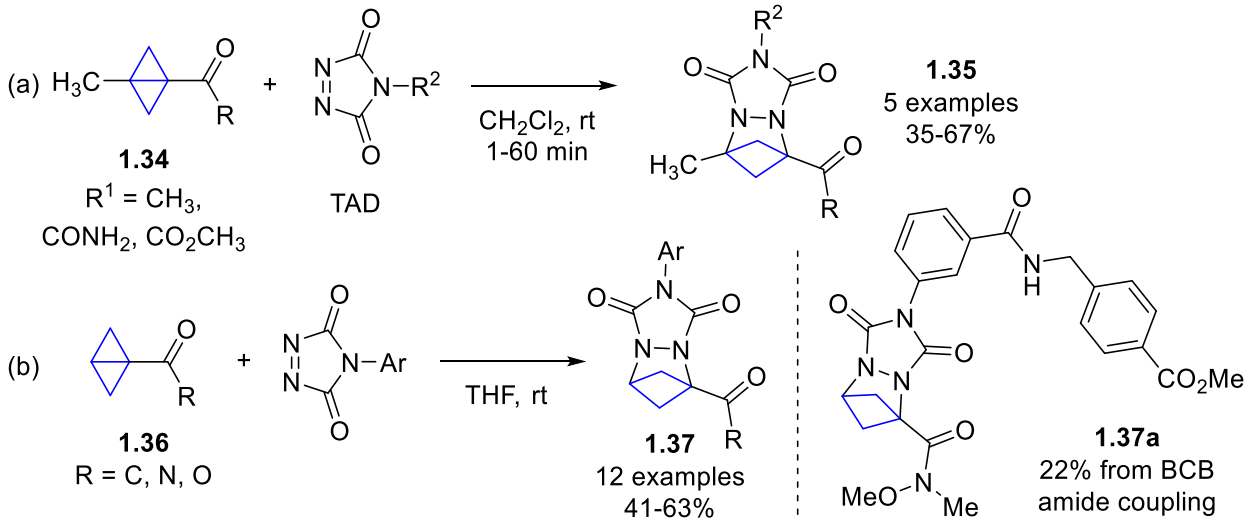
Scheme 1.11 Cycloisomerization of a BCB via rhodium insertion.

In 1964, the pioneering [2+2] cycloaddition of 3-methylbicyclo[1.1.0]butanecarbonitrile was reported to provide bicyclo[2.1.1.]hexanes (BCH) **1.32** in low to moderate yields and low diastereo- and regioselectivities (Scheme 1.12).[53] Photochemical conditions for the [2+2] cycloaddition with styrene were recently reported.[54]



Scheme 1.12 Synthesis of bicyclo[1.1.2]hexane via cycloaddition on a BCB.

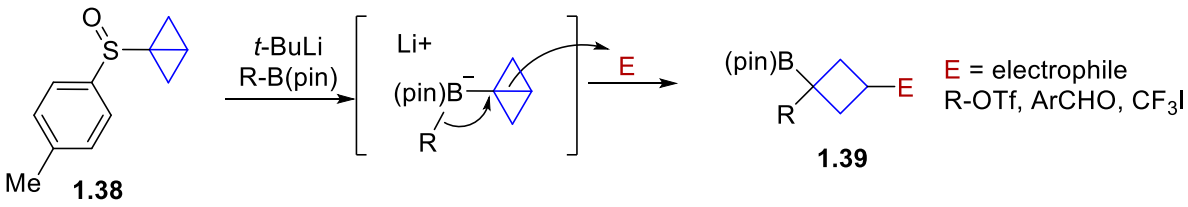
In 1981, 1,2,4-triazole-3,5-diones (TADs) were used in a [2+2] cycloaddition reaction with BCBs.[55] 1-Methyl-3-substituted BCB **1.34** provided cycloadduct 1,3-diazetidine **1.35** almost spontaneously with TADs (Scheme 1.13a). The "click"-like conditions were slightly modified by Malins in the functionalization of amides, such as in **1.37a** (Scheme 1.13b).[56]



Scheme 1.13 Hetero[2+2]cycloadditions to BCBs.

1.2.3.3 Electrophilic Addition

Precedent for electrophilic additions to BCBs is currently limited to bicyclo[1.1.0]butyl boronate **1.38**, where a negatively charged boronate activates additions (Scheme 1.14). Upon activation with *t*-BuLi, electrophiles such as triflates,[57] aldehydes,[58] and trifluoromethyl iodide[59] were successfully added to BCBs to provide trisubstituted cyclobutanes **1.39**.



Scheme 1.14 Electrophilic addition on a BCB.

Although BCBs were exploited in further transformations, those requiring specific substituents[41,60] and providing acyclic products[61] will not be discussed. The subsequent chapters will explore the preparations of the BCB group, which are classified as proceeding via transannular ring closure, cyclization of cyclopropyl lithium species, and cyclopropanation of an appropriately unsaturated compound. While BCB syntheses will be discussed in chapter 3, the preparation of the requisite cyclopropane will be discussed first.

1.3 Cyclopropane Synthesis

Extensive effort has been made to achieve access to highly substituted cyclopropanes in single steps with high yields.[62] Cyclopropane syntheses are classified into three types; those using free or metal carbenes, those using carbenoids, and those using cyclization via addition-elimination processes (Figure 1.10).[63] The latter reaction termed Michael Initiated Ring Closure (MIRC) consists of the 1,4-addition of a nucleophile onto a Michael acceptor. The resulting carbanion is stabilized by a neighboring electron-withdrawing group (EWG) and the anion then undergoes ring closure via displacement of a leaving group, which is often on the nucleophile or sometimes on the alkene.

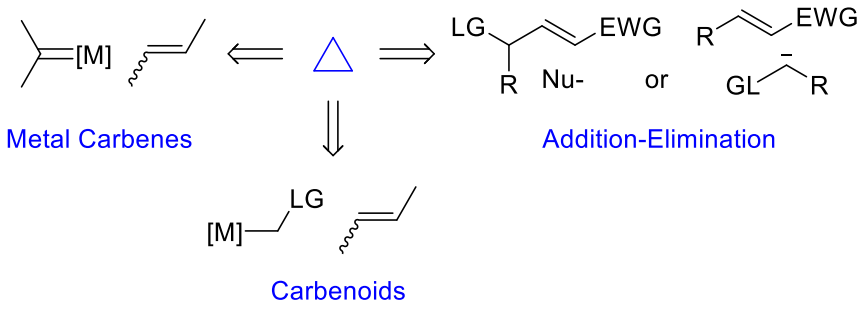


Figure 1.10 Retrosynthetic strategies toward cyclopropanes.

1.3.1 The Use of Metal Carbenes in Cyclopropane Synthesis

A carbene is a neutral entity with a general :CR_2 formula in which the sp^2 carbon is divalent. Carbenes are classified into two categories; Fisher carbenes and Schrock carbenes.[64] Fisher carbenes are often called singlet state carbenes due to their electronic structure, which consists of a two-electron occupied orbital and an empty *p* orbital (Figure 1.11). Schrock carbenes are recognized as triplet state carbenes for the same electronic structure reasons, as the two electrons are unpaired and occupy two different orbitals. While a Fischer carbene can either exist in its free form or be stabilized by a metal, it generally reacts by accepting electrons in its empty *p* orbital, making it electrophilic. Conversely, Schrock carbenes possesses a nucleophilic character with their one-electron *sp* orbital. While a carbenoid is an electrophile as well,[65] carbenoids and carbenes are distinct species that are often mistakenly confused in the literature.[66] On a carbenoid, the anti-bonding molecular orbital of the sp^3 carbon bearing a leaving group (LG) is attacked by the alkene during cyclopropanation.

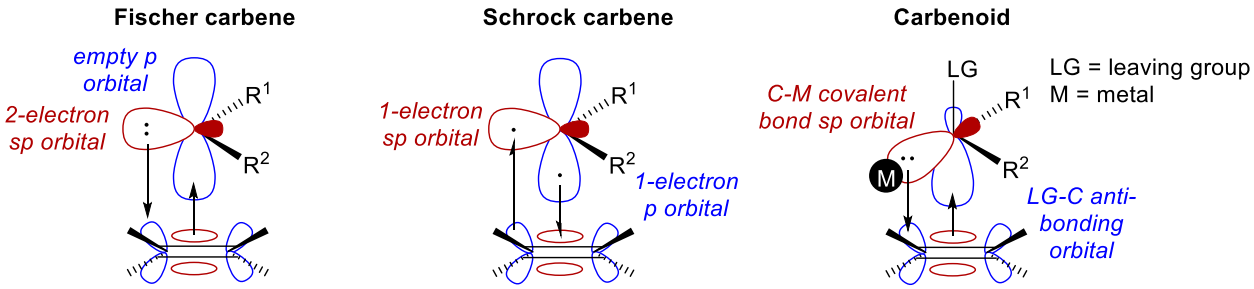
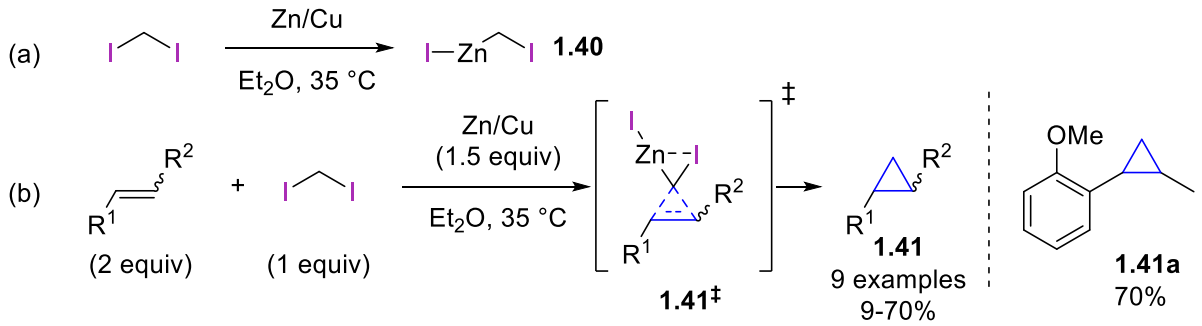


Figure 1.11 Metal carbene and carbenoid representations and their interactions with alkenes.

1.3.2 The Use of Carbenoids in Cyclopropane Synthesis

1.3.2.1 General Information on Carbenoids

In 1929, Emschwiller reported the first synthesis of (iodomethyl)zinc iodide **1.40** using zinc/copper on diiodomethane (Scheme 1.15a).[67] Three decades passed until Simmons and Smith discovered the power of cyclopropanation when they combined Emschwiller's conditions with alkenes (Scheme 1.5b).[68] Since then, entity **1.40** has been referred to as the Simmons-Smith carbenoid.[63] The seminal publication included a 2-methoxyphenyl-substituted substrate which furnished an outstanding 70% yield of cyclopropane **1.41a** despite being one of the most hindered substrates.[68] The mechanism was proposed to proceed via a concerted [2+1] cyclization with a "butterfly-like" transition state **1.41‡**. This transition state is generally well-accepted as it in accordance with the stereospecificity of the reaction and the starting material stereochemistry. Coordination of the zinc carbenoid with an alcohol inspired the first diastereoselective version of the Simmons-Smith reaction, which capitalizes on the Lewis acidity of the zinc metal center.[69] The coordination later became a keystone for the development of enantioselective methods.[70]

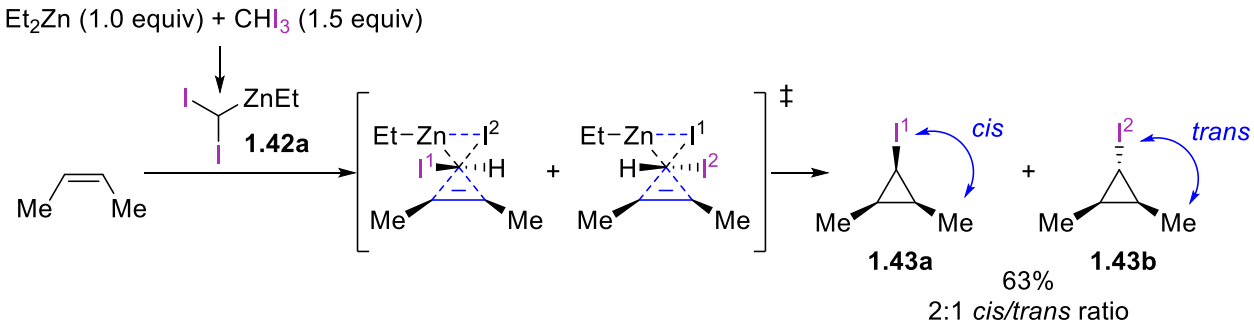


Scheme 1.15 Simmons-Smith cyclopropanation.

Modification of carbenoid **1.40** altered its reactivity, expanding the scope in various processes.[63] For instance, Furukawa replaced the zinc/copper couple with diethyl zinc.[71] Despite its high pyrophoricity, employing diethyl zinc was beneficial by negating the need for coordinating solvents and affording better control over the stoichiometry due to its liquid state.[72]

1.3.2.2 Iodocyclopropanations *via* a Monozinc Carbenoid

Varying the substitution of a carbenoid can alter its reactivity and in many cases, help expand the scope of substituted cyclopropanes available.[63] When diiodomethane is replaced with iodoform, diiodocarbenoid **1.42a** is obtained and one of the iodine from the iodoform reagent is transferred to the cyclopropane to furnish iodocyclopropanes (Scheme 1.16). The approach employed various haloforms and was initially studied by Furukawa.[73] The reaction was later optimized using the substrate as the solvent, drastically improving yields.[74] When *cis*-2-butene was submitted to iodocyclopropanation conditions, the most hindered *cis*-cyclopropane **1.43a** was obtained as the major product. A 2:1 *cis/trans* ratio of **1.43a/1.43b** was observed, leading to a postulate that the diastereoselective outcome of the reaction is dictated by two structurally distinct transition states.[75]



Scheme 1.16 Diastereoselective iodocyclopropanation using iodoform.

Following the exploration of iodocyclopropanation, it was demonstrated that the presence of zinc salts, which are by-products of the cyclopropanation as well, enhanced the rate of the reaction. Another transition state (Figure 1.12) was proposed based on theoretical calculations, in which Lewis acid zinc salts (in red) would activate the leaving group of the carbenoid (in blue) during the cyclopropanation of the allylic alcohol.[76]

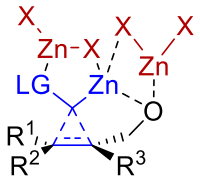
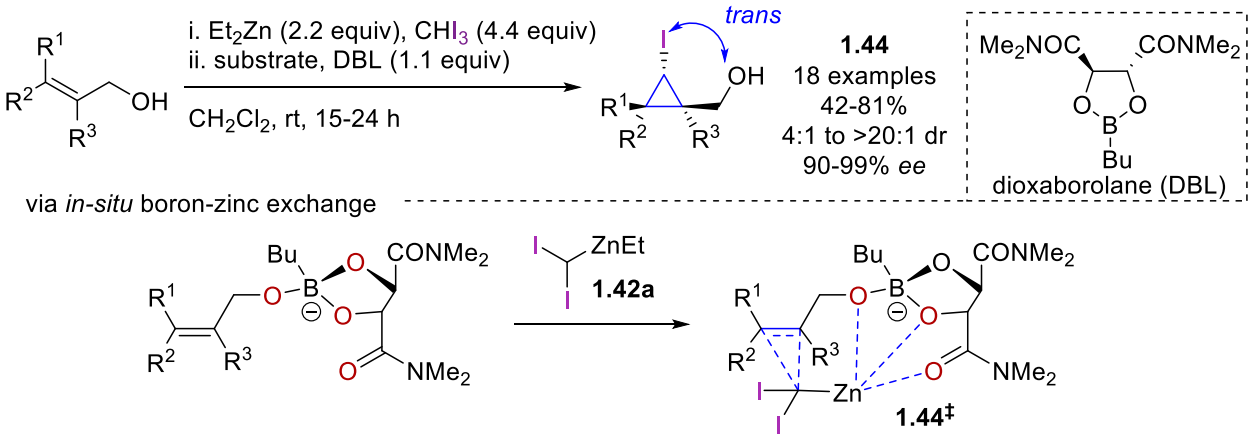


Figure 1.12 Calculated transition state for the iodocyclopropanation using zinc additives.

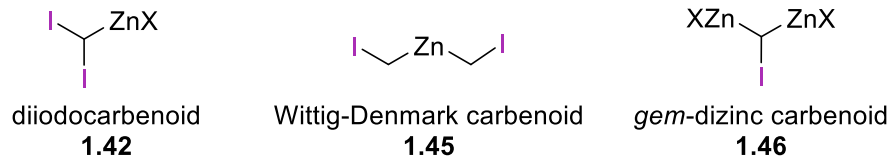
Dr. Louis-Philippe B. Beaulieu, a former Charette group member, developed the first enantioselective synthesis of iodocyclopropanes **1.44** starting from allylic alcohols and using diethyl zinc and iodoform in a 1:2 ratio (Scheme 1.17).[77] Employing the previously developed chiral auxiliary dioxaborolane (DBL)[78] to leverage the suggested transition state allowed access to *trans*-iodocyclopropylmethanols **1.44** with enantioselectivities higher than 90% in all substrates.[77] Upon pre-coordination of the substrate allylic alcohol and the boron of the chiral ligand, the zinc metal center from the carbenoid **1.42a** could coordinate to the oxygen atom of dioxaborolane, thus bringing the zinc on the same side of the cyclopropane as the alcohol and leaving the remaining iodine on the opposite side (**1.44‡**). The formation of the *cis*-cyclopropane was unlikely since the zinc atom would not coordinate to the alcohol in the corresponding transition state.[77] Although the method afforded the desired iodocyclopropanes **1.44** in good yields, it suffered from the superstoichiometric use of iodoform.



Scheme 1.17 Beaulieu's iodocyclopropanation method.

In carbenoid quenching experiments, significant amounts of iodoform were recovered, refuting the $(Zn(CHI_2)_2$ carbenoid **1.45** formation postulate based on the 1:2 stoichiometry of zinc/iodoform (Figure 1.13). Carbenoid **1.45** is also recognized as the Wittig-Denmark carbenoid.[79]

Therefore, diiodocarbenoid $I_2CHZnEt$ **1.42a** was postulated instead, as it can still be theoretically prepared from a 1:1 ratio. When the hypothesis was tested using a 1:1 ratio of diethylzinc and iodoform, only a modest 62% yield of iodocyclopropane **1.44** was obtained along with the remaining 14% starting material. Increasing the stoichiometric ratio of Et_2Zn relative to CHI_3 resulted in a decreased proportion of the α-iodozinc carbenoid **1.42** relative to the *gem*-dizinc carbenoid **1.46**, a species that will be further discussed in the next section.

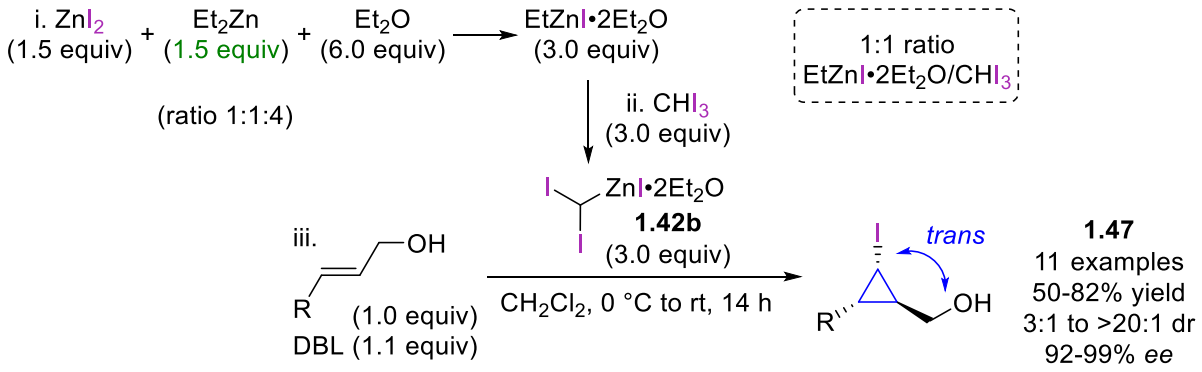


diiodocarbenoid **1.42** | Wittig-Denmark carbenoid **1.45** | *gem*-dizinc carbenoid **1.46**

Figure 1.13 Wittig-Denmark and Furukawa carbenoids.

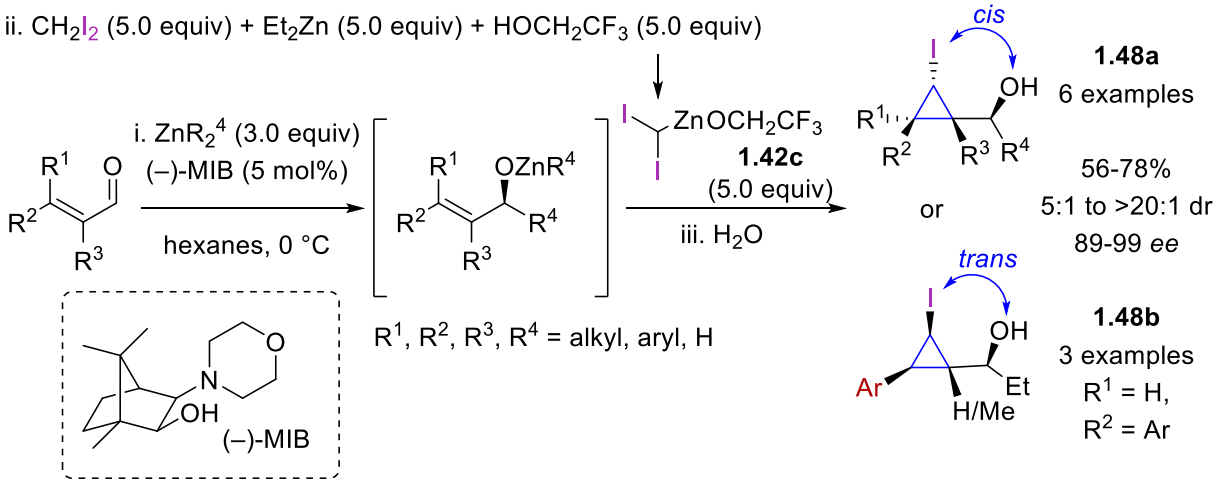
Dr. Sylvain Taillemaud, a former Ph.D. Charette group member, eventually improved the stoichiometry in zinc carbenoids.[80] Preliminary studies revealed that the theoretically optimal 1:1 ratio of zinc/haloform could be obtained by replacing diethyl zinc with ethyl zinc iodide dietherate ($EtZnI•2Et_2O$). The addition of a Lewis base type additive was revealed to be a crucial factor in the formation and stability of monozinc diiodo carbenoids, such as **1.42**.

Haloalkylzinc species can be generated according to three classes of reactions.[63] The first one, the most widely used method for the cyclopropanation of simple olefins and employed by Beaulieu, is the oxidative addition of an activated form of zinc metal into a carbon−halogen bond. Haloalkylzinc species can also be obtained from the alkyl group exchange between an organozinc reagent and a dihaloalkane or the insertion of a diazoalkane into a zinc-iodide bond. The latter alkyl group exchange mechanism as well as the introduction of diethyl ether to form ethyl zinc iodide dietherate was leveraged in an improved synthetic route to *trans*-iodocyclopropylmethanols **1.47** (Scheme 1.18).[18] Upon *in situ* generation of ethyl zinc iodide dietherate from zinc iodide/diethyl zinc/diethyl ether in a relative ratio of 1:1:4 followed by the addition of iodoform in a 1:1 ratio, the desired diiodocarbenoid I_2CHZnR **1.42b** was obtained after almost complete conversion of iodoform. The method minimized the amount of pyrophoric reagent required by replacing half of the required diethylzinc with zinc iodide. Compared to Beaulieu's method, the yields, functional group tolerance, diastereoselectivity, and enantioselectivity remained similar.



Scheme 1.18 Taillemaud's iodocyclopropanation of allylic alcohols.

Considering the aforementioned advances toward *trans*-iodocyclopropanes **1.47**, the use of zinc carbenoids is the most straightforward method to obtain iodocyclopropanes when compared to other strategies. In related work, both *cis*-iodocyclopropanes **1.48a** and *trans*-iodocyclopropanes **1.48b** could be generated from a tandem asymmetric organozinc addition on enal derivatives directed by the chiral ligand (2*S*)-3-*exo*-(morpholino)isoborneol ((−)-MIB) (step i), followed by an iodocyclopropanation (step ii) to give the resulting cyclopropanes **1.48a** and **1.48b** with excellent enantioselectivity and good yields (Scheme 1.19).[81] During the cyclopropanation, a mono-zinc diiodocarbenoid **1.42c** was formed from a 1:1:1 relative ratio of diethylzinc, diiodomethane and 2,2,2-trifluoroethanol. 2,2,2-Trifluoroethanol was proposed to increase the carbenoid reactivity.



Scheme 1.19 Walsh's iodocyclopropanation of enals.

Interestingly, *cis*-cyclopropanes **1.48a** were obtained for β-alkylenals whereas *trans*-cyclopropanes **1.48b** were obtained for β-aromatic enals. To rationalize the stereochemical

outcome, transition states involving weak coordination between the iodine and the zinc from the zinc alkoxide, were postulated for *cis*-cyclopropanes **1.48a‡** (Figure 1.14a, in red). However, on aromatic enals, π-stacking with an external zinc carbenoid and the interaction of the external zinc with the iodine from the carbenoid seemed to be dominant in **1.48b‡** (Figure 1.14b, in red), thus reversing the stereoselectivity.[82]

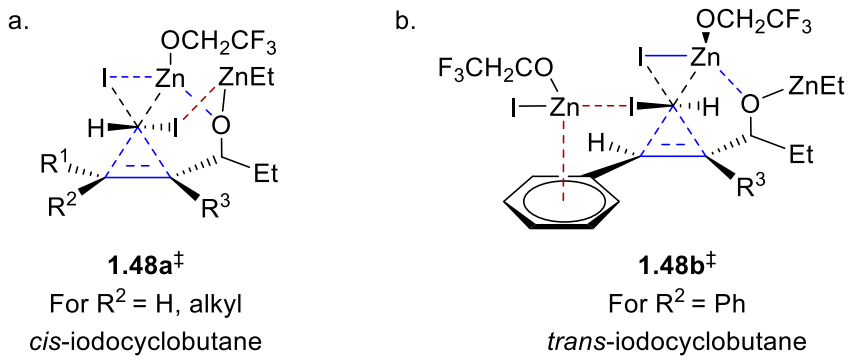
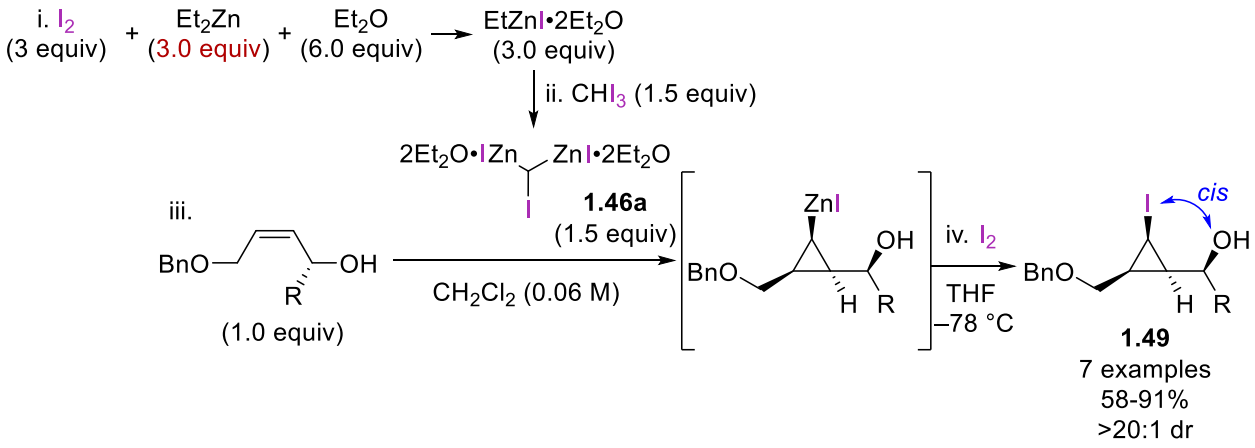


Figure 1.14 Proposed transition states of Walsh's cyclopropanation of enals.

1.3.2.3 Zincocyclopropanation via *gem*-Dizinc Carbenoids

Another possible modification on carbenoids is the addition of one more equivalent of zinc, specifically a 2:1 relative ratio of zinc to iodoform, which enables access to a *geminal*-dizinc carbenoid **1.46a** (Figure 1.13).[83] The reactivity of the *gem*-dizinc carbenoid **1.46a** with various alkenes was leveraged in the synthesis of *cis*-iodocyclopropanes **1.49** in Dr. Jean-François Fournier's Ph.D. research (Scheme 1.20).[84] Excellent diastereoselectivity, as well as good to excellent yields, were obtained. The cyclopropylzinc intermediate can be quenched by a variety of electrophiles, such as water, deuterium oxide, bromine, aldehydes, aryl halides, and acid chlorides.[84] Seven examples of *cis*-iodocyclopropanes **1.49** were prepared using the conditions (Scheme 1.20), where the previously-employed dioxaborolane ligand was replaced by another chelating group on the substrate. The term "iodocyclopropanation" is used for the transformation of an alkene to an iodocyclopropane using a diiodomethylzinc carbenoid. Conversely, the term "zincocyclopropanation" is used when a *gem*-dizinc iodomethyl carbenoid is involved, although formation of an iodocyclopropane is possible.



Scheme 1.20 Fournier's zincocyclopropanation of allylic alcohols.

In the postulated transition state, the zinc metal from the carbenoid coordinates to both the benzyl ether and the alkoxide of the substrate, rationalizing the stereochemical outcome (Figure 1.15).[85] The deprotonation of the alcohol by an external ethylzinc iodide dietherate allows additional coordination in favor of the *cis* configuration. Although excellent diastereoselectivity was obtained, products were isolated as racemates.

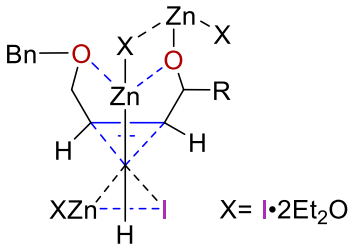
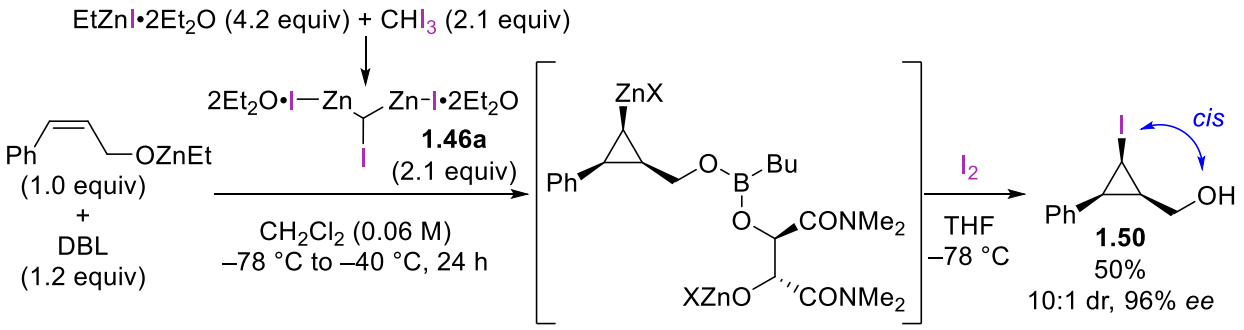


Figure 1.15 Proposed zincocyclopropanation transition state.

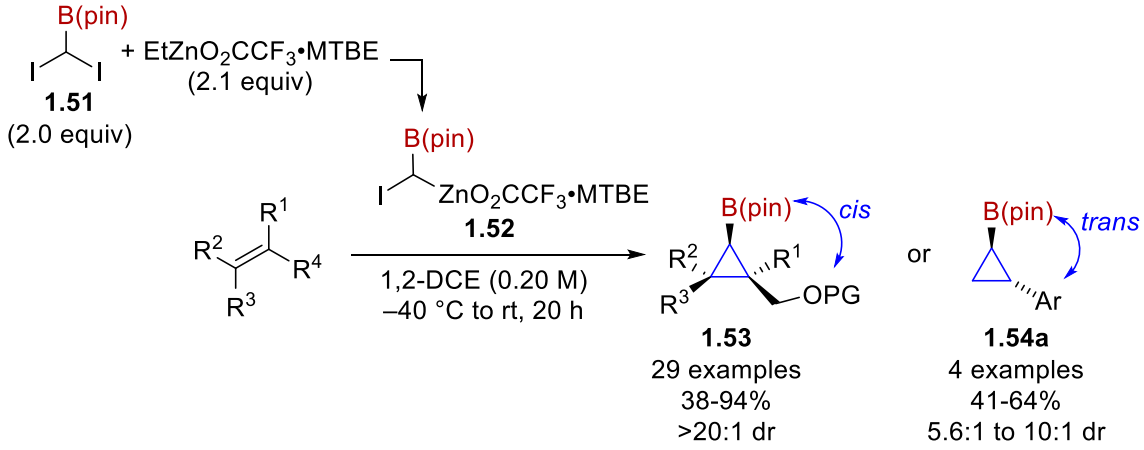
To mitigate the requirement of the second directing group and the lack of enantioselectivity, the dioxaborolane ligand was included in the zincocyclopropanation conditions (Scheme 1.21). *cis*-Cinnamyl alcohol underwent zincocyclopropanation under the reaction conditions and, upon treatment with iodine, iodocyclopropane **1.50** was obtained in good yield and excellent enantioselectivity, albeit lower diastereoselectivity (Scheme 1.21).[86] It was observed that preliminary deprotonation of the alcohol with diethylzinc, instead of the *gem*-dizinc carbenoid, was mandatory to prevent the formation of the Simmons-Smith carbenoid $IZnCH_2I$ **1.40** (Scheme 1.15). Although the carbenoid precursor is not limited to haloforms,[87] the research presented in the thesis focuses on zincocyclopropanation using iodoform, thus other precursors will not be presented.



Scheme 1.21 Enantioselective zincocyclopropanation of *cis*-cinnamyl alcohols.

1.3.2.4 Borocyclopropanation using Zinc Carbenoids

As substitution of the ligands on carbenoids afforded new cyclopropanation methods, a borocyclopropanation using the zinc borocarbenoid **1.52** was developed by Dr. Guillaume Benoit, a former Ph.D. Charette group member (Scheme 1.22).[88] In the method, coordination of the zinc carbenoid and the allylic ether of the substrate led to *cis*-cyclopropane **1.53** in an excellent ratio of diastereomers without a ligand. Conversely, the borocyclopropanation of styrenes provided *trans*-borocyclopropanes **1.54a** with lower diastereoselectivity, due to the lack of coordination between the substrate and the zinc reagent.

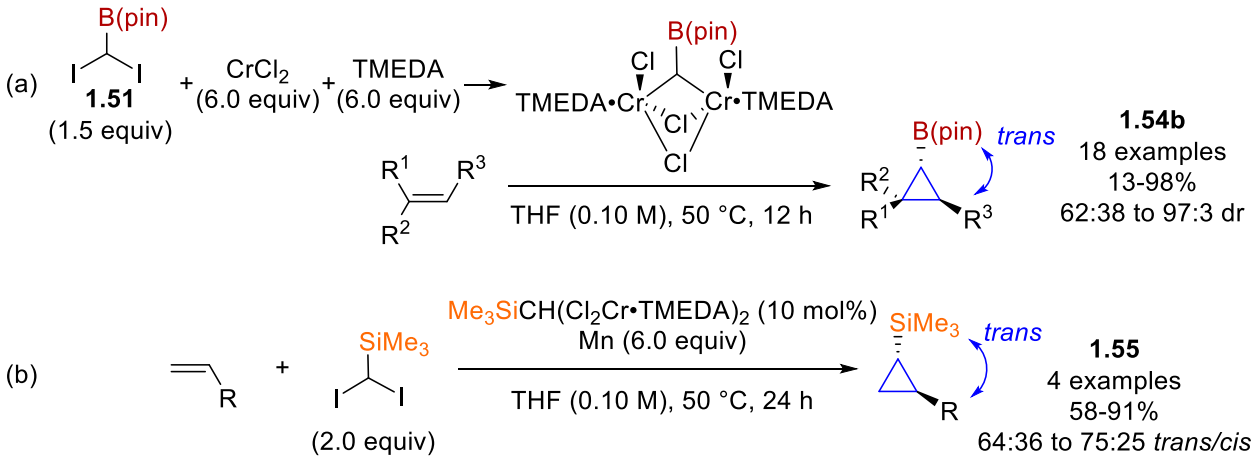


Scheme 1.22 Benoit's borocyclopropanation of alkenes.

1.3.2.5 Boro- and Silylcyclopropanation via Chromio Carbenoids

Although zinc carbenoids are popular reagents, carbenoids can also be prepared from other metals, such as chromium.[89] Chromio carbenoids have been used in iodocyclopropanations, in addition to have been exploited for the synthesis of borocyclopropanes **1.54b** and

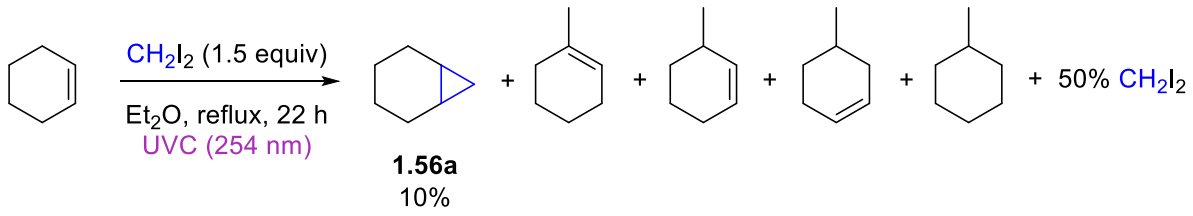
silylcyclopropanes **1.55** (Scheme 1.23).[90] Initially, methods employed an organochromium reagent generated from the corresponding carbene precursor ($I_2CHB(pin)$ or $I_2CHSiMe_3$), and stoichiometric amounts of chromium chloride. A *gem*-dichromio carbenoid synthesized from a 1:4:4 relative ratio of carbene precursor, chromium chloride, and ligand, was postulated to be the major cyclopropanation reagent (Scheme 1.23a).[91] *N,N,N'N'*-Tetramethylethylenediamine (TMEDA), used as the ligand on chromium, was required for the reaction to take place. Both borocyclopropanation and silylcyclopropanation were developed, the latter was later optimized to use catalytic quantities of chromium with manganese metal as the stoichiometric reductant (Scheme 1.23b).[92] Although *gem*-dimetallic carbenoids were used, the lack of interaction between the substrate and the carbenoid resulted in mostly *trans*-cyclopropane products (**1.54b** and **1.55**). Despite the efficiency of the methods, the use of toxic chromium reagents limits their applicability.



Scheme 1.23 Chromiocarbenoid-mediated boro- and silyl-cyclopropanations.

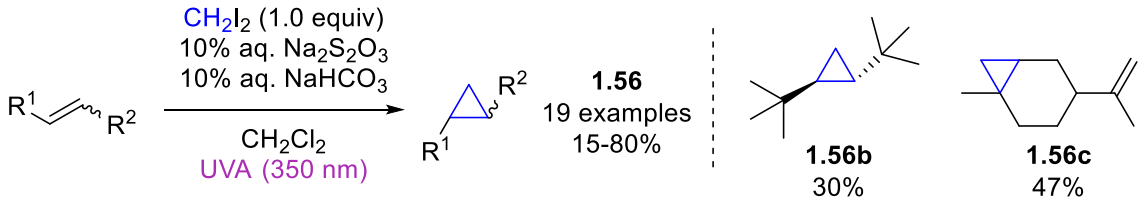
1.4 Cyclopropanation in Photochemistry

The power of radiant energy was recognized by Ciamician in his famous article "The Photochemistry of the Future" in 1912.[93] Inspired by the blueprints of light-harvesting biomolecules, chemists started to exploit the benefits of the abundant and safe energy from light only in the last century.[94] The first photochemical cyclopropanation, using a low-pressure mercury lamp in a quartz flask ($\lambda = 254$ nm, UVC) was reported by Simmons in 1965 (Scheme 1.24).[95]



Scheme 1.24 Pioneering attempts at photochemical cyclopropanation.

A decade later, Kropp developed a method in which the scope and yields were significantly improved, but still suffered from drawbacks that accompanied UV light (Scheme 1.25).[96] Interestingly, *cis*-, *trans*- and trisubstituted-alkenes reacted under the reaction conditions. The relative lack of sensitivity to steric effects of the photocyclopropanation is an advantage compared to the zinc carbenoid procedure. For instance, in an example where a zinc carbenoid cyclopropanation was totally ineffective, 30% of 1,2-di-*t*-butylcyclopropane **1.56b** was obtained using photochemical cyclopropanation of *trans*-di-*t*-butylethylene.[97] Another interesting change in reactivity was observed in the cyclopropanation of limonene. While the most hindered double bond reacted more rapidly under photochemical conditions to produce **1.56c**, the cyclopropanation under Simmons-Smith conditions only occurred on the least hindered alkene. Many examples in which the two methods (Simmons-Smith and photochemical cyclopropanation) are synthetically complementary can be found in the literature.[97]



Scheme 1.25 Photochemical cyclopropanations of hindered alkenes.

The progress of photochemical cyclopropanation was limited as most organic compounds only absorb in the ultraviolet region of the solar spectrum.[98] Despite UV photoreactors being designed to utilize UV light in synthesis, major drawbacks, such as the need for specialized expensive glassware, protective gear, and high-power consumption dissuaded popular use of photochemistry. Alternative methods taking advantage of visible light are therefore highly in demand.[99] Transition-metal photocatalysts, which are more likely to absorb light in the visible region, obviated many of the challenges associated with photochemistry high energy

wavelengths.[100] In addition, significant advances over the last 40 years allowed chemists to exploit visible-light absorbing metal-free photocatalysts, such as organic dyes.[101] Recent interest in sustainability has encouraged research into metal-free photocatalysis.[102] In the following section, fundamental principles of photochemistry as well as examples of photocatalysis will be introduced. Selected examples of photochemical cyclopropanations will be illustrated.

1.4.1 Fundamentals of Photochemistry

Photochemistry is defined by physical changes and the study of chemical reactions occurring under the absorption of light by atoms and molecules.[98-102] Each molecule has a maximum absorption wavelength (λ_{max}) that can be determined by measuring its UV-visible spectrum. For organic molecules, that value is typically in the ultraviolet (≈100-400 nm) or the visible light ranges (380-750 nm). Whereas photochemical reactions generally occur within those ranges, examples of infrared-promoted photochemistry have been reported.[103] Microwave irradiations, albeit having other applications in chemistry, do not provide enough energy for photochemical transformations (Figure 1.16).

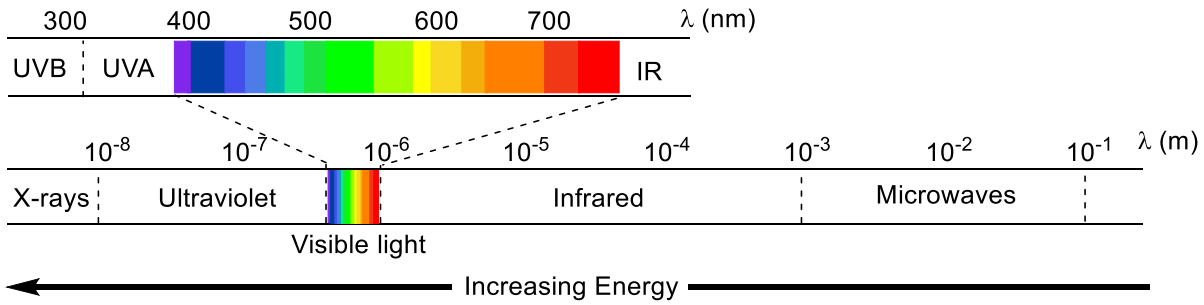


Figure 1.16 The electromagnetic spectrum.

Light can be monochromatic or polychromatic. White light and sunlight, containing all the wavelengths of the visible light spectrum, are examples of polychromatic light. To ensure that the maximum number of reactant molecules can access their excited state and to maximize the absorption of a molecule, the chosen working light source must emit photons having a wavelength as close as possible to its λ_{max}.[104]

The absorption of light, which corresponds to the capture of a photon by a molecule, can provide the required activation energy to promote reactions that are not accessible thermally.[100] The phenomena can be explained by the principles of molecular orbital theory (Figure 1.17a). The

highest occupied molecular orbital (HOMO) is usually where paired electrons exist at their ground singlet state (S_0) whereas the lowest unoccupied molecular orbital (LUMO) is the next lowest energy empty orbital. Upon irradiation and absorbance of a photon (abs), one electron from the HOMO jumps into the next empty orbital (LUMO) and the orbital becomes the HOMO*. The new electron configuration is defined the excited singlet state (S_1), in which both unpaired electrons still possess their initial spin. Upon intersystem crossing (ISC), the electron in the HOMO* switches spin state to reach the triplet excited state (T_1). Both unpaired electrons in S_1 and T_1 can undergo single electron transfer (SET) or energy transfer (ET). Energy transfer can proceed by releasing heat or it can lead to a productive photocatalytic transformation.

The Jablonski diagram in Figure 1.17b illustrates electronic transitions. Upon absorption of light, the excited electron at S_1 can pursue different deactivation pathways. The first option is to return to the ground state and regenerate the photocatalyst either by releasing heat (via non-radiative internal conversion, k_{iC}) or by a spin-allowed radiative pathway, which defines fluorescence (k_F). If the electron converts to T_1 through intersystem crossing (ISC), the electron is less transient than at its singlet state, because its reversal to S_0 is spin forbidden. From the triplet state, three pathways are available. It can either return to the ground state via internal conversion (k_{iC}) or by radiative deactivation, which is characterized as phosphorescence (k_P). The third option is to transfer the energy to a chemical reagent (electron transfer, k_{ET}), which can lead to a productive photocatalytic transformation.

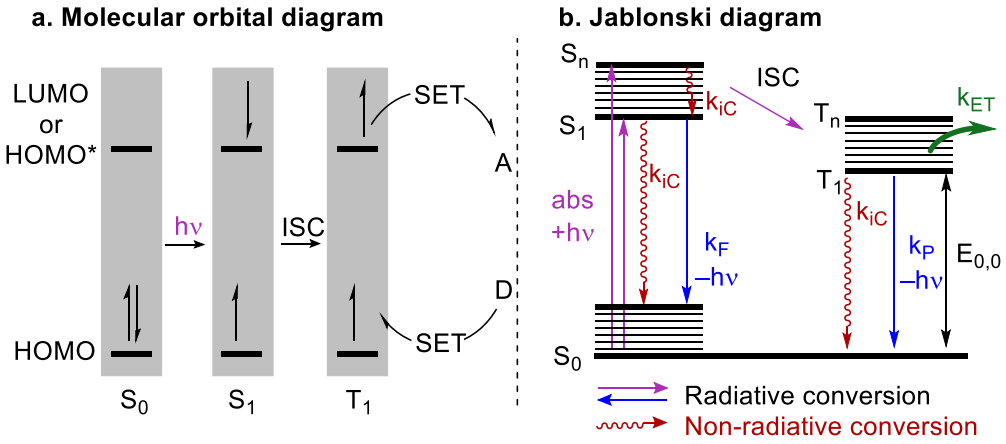


Figure 1.17 Molecular orbitals and simplified Jablonski diagram.

1.4.2 Photocatalysis and Photoredox Catalysis

Photocatalysis is defined as a process in which the absorption of light accelerates the rate of a reaction.[101-105] Most photoredox-mediated transformations are enabled using transition-metal- and organic-based photocatalysts, which are active at excited states (T_1 or S_1). From the excited states, the photocatalyst can go through energy transfer or single electron transfer with a compatible donor or acceptor.

Initial contributions from MacMillan,[105] Yoon,[106] and Stephenson[107] underscored the potential of photocatalysis for method development in organic synthesis using ruthenium and iridium polypyridyl complexes. Some organic molecules, such as organic dyes, have been known to absorb light for decades. Considering the high cost and low sustainability of transition metal-based photoredox catalysts, organocatalysts are preferable (Figure 1.18). Photocatalysts have been modulated to obtain specific photophysical properties including specific absorption and emission wavelengths, redox potentials, and excited-state lifetimes. The range of synthetic transformations accessible through photoredox catalysis has grown with the diversity of catalysts.[108] Among the metal-free catalysts developed over the years, higher yields were generally obtained when using the organic dye Eosin Y, compared to other organic dyes of the fluorescein family.[109]

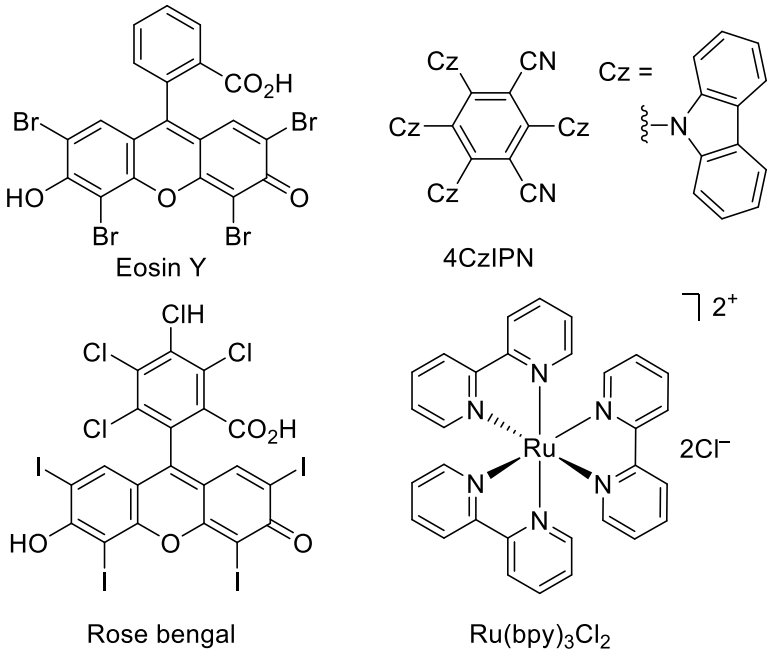


Figure 1.18 Selected photoredox catalysts.

Photochemical single electron transfer reactivity can occur via oxidative and reductive quenching mechanisms.[107] For instance, absorption of visible green light (λ_{max} = 520 nm) in Eosin Y promotes *Eosin Y to its excited state (Figure 1.19). *Eosin Y undergoes rapid intersystem crossing (ISC) to the lowest energy triplet state, which has an excited-state lifetime of 2400 ns.[110] The relatively long excited-state lifetime can be explained by the spin rule, which states that returning to the ground state from the triplet state is forbidden without a spin flip. Most photocatalysts perform their electronic transfers from their triplet state.[98] Redox-type processes are generally facilitated by long-lived excited states. If a compatible electron acceptor (A) is in the presence of the excited photocatalyst, *Eosin Y can be oxidized by releasing an electron to convert into Eosin $Y^{+\bullet}$ (E^{Ox}_{S1} = –1.58 V vs saturated calomel electrode (SCE)).[111] Eosin Y at its ground state is then regenerated with an appropriate donor ($E^{Ox}_{½}$ = +0.76 V vs SCE). If the photocatalyst is in the presence of a compatible donor (D) instead of an acceptor, *Eosin Y can be reduced by accepting an electron to generate Eosin $Y^{-\bullet}$ (E^{Red}_{S1} = +1.23 V vs SCE). In that case, an appropriate acceptor is required to regenerate Eosin Y at is ground state ($E^{Red}_{½}$ = –1.08 V vs SCE). Depending on the desired chemical transformation and redox potentials of involved reactants, an appropriate photocatalyst can be chosen according to its redox potentials.

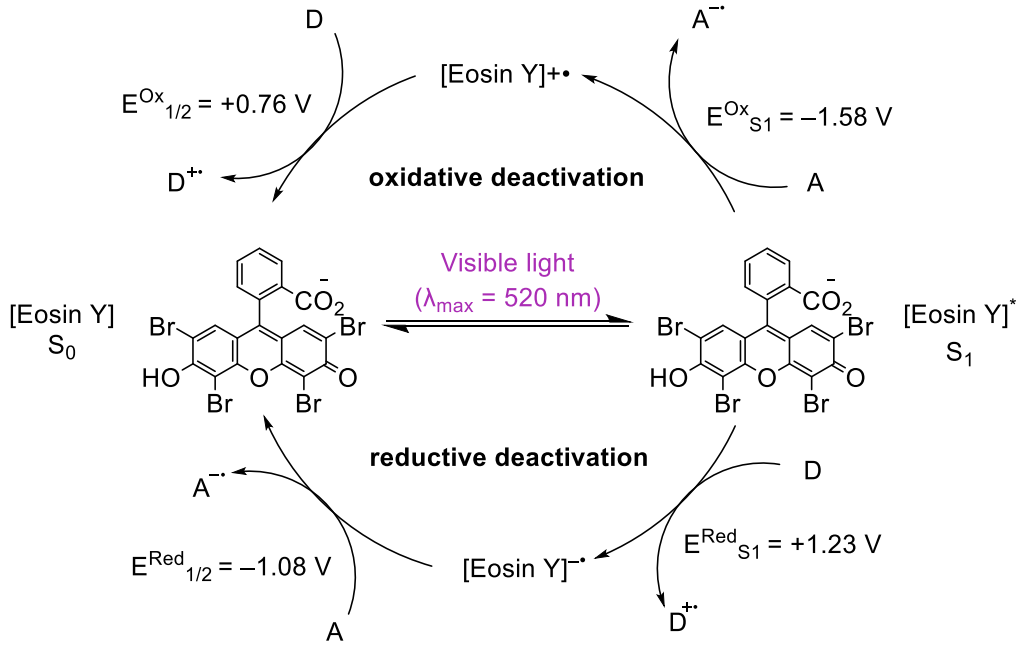
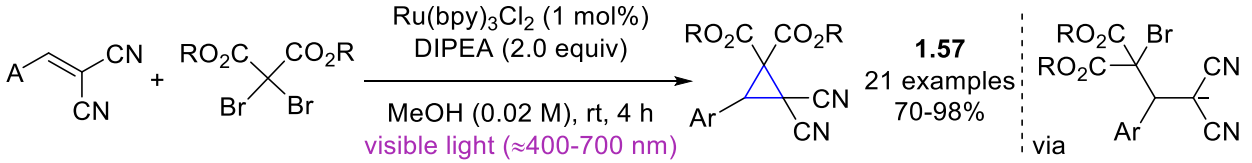


Figure 1.19 Oxidative and reductive catalytic cycles of Eosin Y.

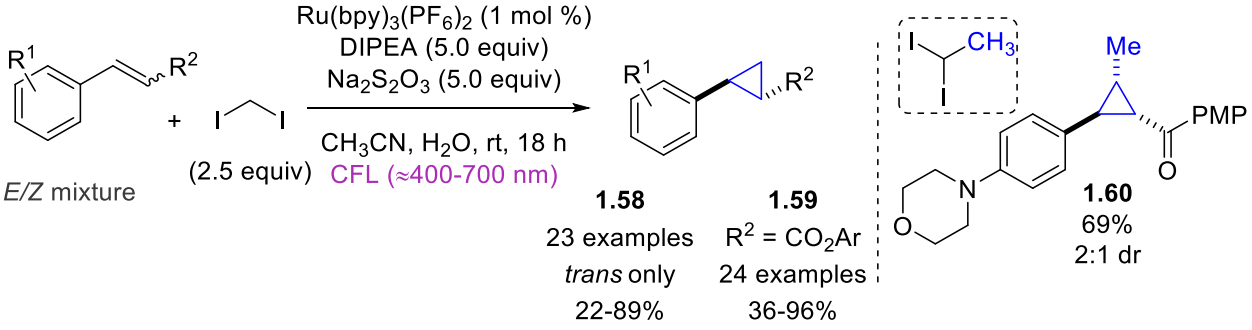
1.4.3 Previous Photocatalyzed Cyclopropanations

The first example of cyclopropanation under catalytic photoredox conditions was reported by Guo and provided highly substituted cyclopropanes **1.57** in excellent yields (Scheme 1.26).[112] In the reaction, upon excitation of $Ru(bpy)_3^{2+}$ using a 23 W household lamp, a single electron transfert (SET) to dibromomalonate would generate a bromomalonyl radical, which undergoes a second SET to form a stabilized carbanion. The anion performs nucleophilic addition for the ring-closing step, which expels the second bromine as a leaving group. Photocatalyzed cyclopropanations of Michael acceptor substrates involving (but not limited to) α,β-unsaturated phosphonates, acrylates, ketones, amides, and sulfones, have been developed using redox neutral conditions.[113] Those examples will not be presented in details, as the thesis focuses on cyclopropanations of non-activated alkenes.



Scheme 1.26 First photocatalyzed cyclopropanation.

Suero developed a ruthenium-photocatalyzed stereoconvergent synthesis of disubstituted cyclopropanes **1.58** or cyclopropylcarboxylates **1.59** from diiodomethane and styrene derivatives[114] or chalcone-type substrates[115] respectively (Scheme 1.27). Sodium thiosulfate was added to neutralize iodinated by-products, which can deactivate the excited states of ruthenium complexes. In one interesting scope entry, diiodomethane was replaced with 1,1-diiodoethane to provide the 1,2,3-trisubstituted cyclopropane **1.60**.[115]



Scheme 1.27 Suero's photochemical cyclopropanations.

When the reaction was carried out on a mixture of *E*- and *Z*-alkenes, *trans*-cyclopropanes **1.58** were selectively formed.[114] Suero's cyclopropanation was proposed to occur via a reductive deactivation cycle according to the ruthenium complex, diiodomethane, and diisopropylethylamine redox potentials (Figure 1.20). Upon irradiation, the excited ruthenium complex is reduced by diisopropylethylamine to afford a $Ru(bpy)_3^+$ species, which in turn reduces diiodomethane via single electron transfer (SET). The resulting iodomethyl radical undergoes a radical addition to the alkene to generate an alkyl radical. While the radical, stabilized by a neighboring aromatic ring or carboxylate group, can go through a reversible C–C bond rotation, the intermediate is more stable when steric hindrance is reduced. Hence, after cyclization, both *E*- and *Z*-alkenes provide *trans*-cyclopropanes **1.58**.

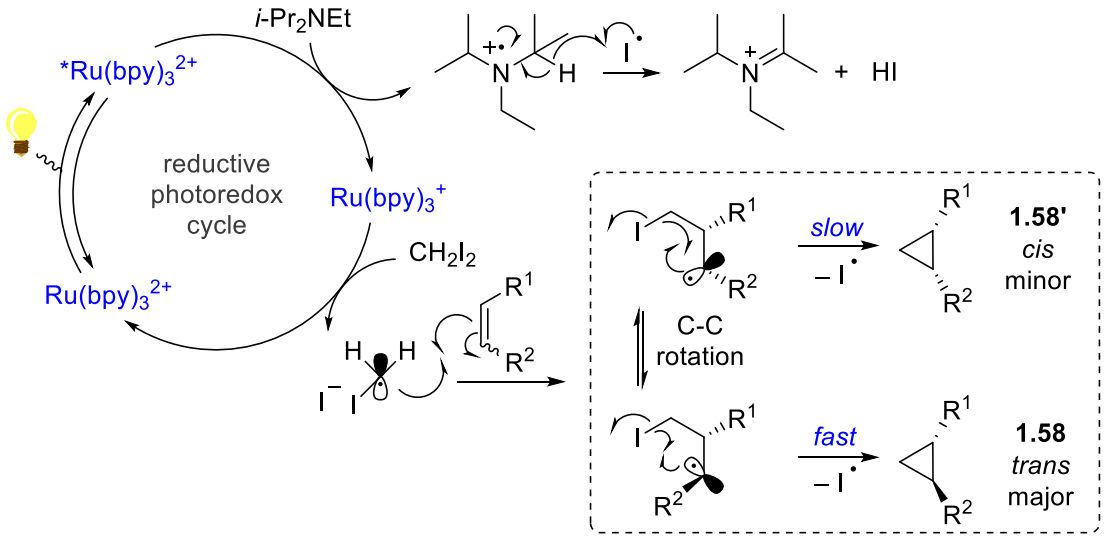
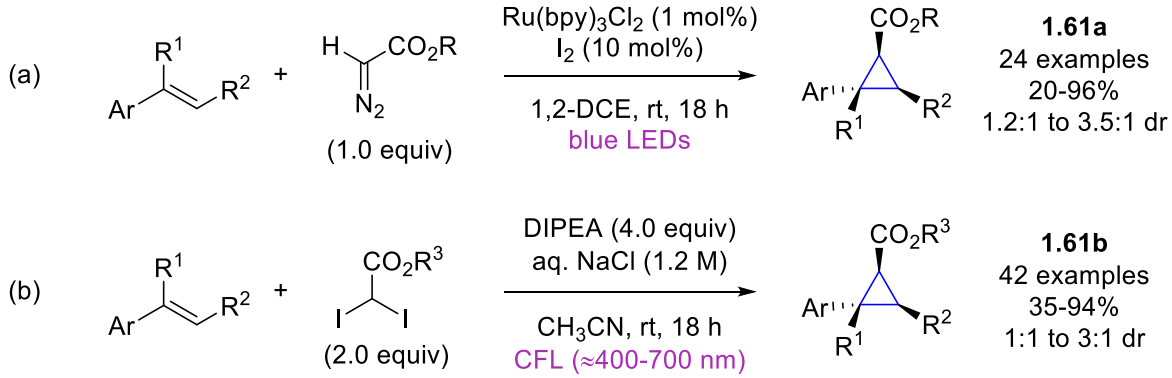


Figure 1.20 Photocatalytic cycle of the Ru-catalyzed cyclopropanation.

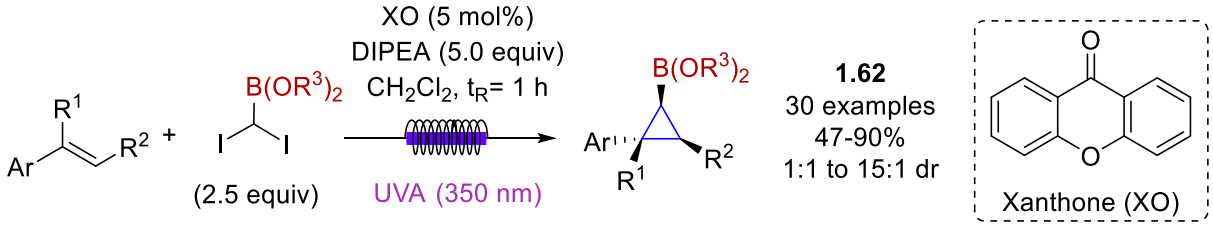
Since nitrogen extrusion acts as an entropically driven process, examples of photocatalyzed cyclopropanations were reported using diazo compounds as carbene precursors and visible light.[116] For example, the photoredox cyclopropanation reaction of alkenes with ethyl diazoacetate using a ruthenium photocatalyst and a catalytic amount of iodine was developed (Scheme 1.28a).[117] The active diiodomethylcarboxylate species was generated *in situ* from ethyl diazoacetate using iodine, which was regenerated at the end. The conditions were applied to a series of variously substituted styrenes with generally excellent yields, albeit low diastereoselectivities, to provide cyclopropyl esters **1.61a**. Since aryldiazoacetates absorb in the visible light region, they were likewise employed in a catalyst-free photocyclopropanation.[118] To circumvent the use of toxic and explosive

diazo reagents, a gram-scale diiodomethylcarboxylate reagent synthesis was developed and used as a carbene precursor for light-mediated cyclopropanation (Scheme 1.28b).[119] While good to excellent yields were obtained under catalyst-free and aqueous conditions, the method provided 1,2,3-trisubstituted cyclopropyl carboxylates **1.61b** with rather poor diastereoselectivities.



Scheme 1.28 Visible-light mediated syntheses of cyclopropyl carboxylates.

Photoredox principles were used in a convenient and scalable mild borocyclopropanation by the Charette group.[120] A xanthone organic photocatalyst, UVA-light (350 nm) and continuous flow technology were used to circumvent the requirement of quartz glassware. Borocyclopropanes **1.62** were obtained in good to excellent yields, albeit with modest diastereoselectivity (Scheme 1.29).



Scheme 1.29 Photochemical borocyclopropanation.

The research objectives of the thesis are aligned with one of the key themes of the Charette research group, which is the development of strategies for the synthesis and functionalization of cyclopropanes. The work presented in chapters 2, 4, and 5 will present the synthesis of iodo- and borosilyl-cyclopropanes respectively while the synthesis of bicyclo[1.1.0]butanes will be the subject of chapter 3.

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2. Development of a Zincocyclopropanation using Bromoform as the Carbenoid Source

2.1 Previous Work and Preliminary Results

2.1.1 Previous Work on Zincocyclopropanation with One Directing Group

Among the strategies leading to *cis*-iodocyclopropanylmethanols, the most recently developed zincocyclopropanation conditions involve only one directing group. Dr. Lucie Zimmer, a former Ph.D. Charette group member, developed conditions in which ethylzinc iodide dietherate was prepared from diethylzinc, iodine, and diethyl ether in a 1:1:2 relative ratio (Figure 2.1, step i).[121] The resulting 4.4 equiv of $EtZnI•2Et_2O$ is available to form 2.2 equiv of the desired *gem*-dizinc carbenoid **2.2a** upon the addition of iodoform (Figure 2.1, step ii). It was observed that preliminary deprotonation of the alcohol **2.1** with diethylzinc was mandatory (step iii) to prevent degradation of the carbenoid and formation of by-products, such as the Simmons-Smith ICH_2ZnX carbenoid. The resulting zinc alkoxide **2.1'** would result in cyclopropylzinc formation upon cyclopropanation with *gem*-dizinc carbenoid **2.2a** (step iv). The protocol was conducted at –40 °C to prevent degradation of the unstable *gem*-dizinc carbenoid **2.2a**. Adding iodine to the organozinc intermediate, followed by an acidic quench to decomplex the zinc alkoxide lead to desired *cis*-iodocyclopropane **2.3** (steps v and vi).

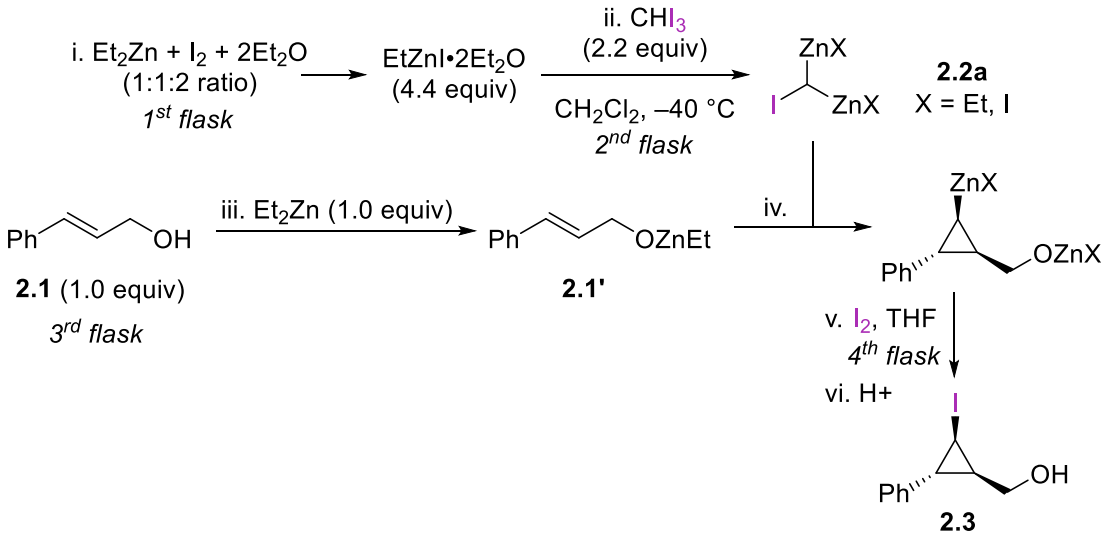


Figure 2.1 Zimmer's zincocyclopropanation protocol of cinnamyl alcohol.

Given that the stability and the reactivity of zinc carbenoids and zinc alkoxide reagents are sometimes capricious, the formation of side products is possible. The rigid exclusion of moisture and the appropriate reagent stoichiometry and addition sequence should be strictly followed to prevent the formation of side products (Figure 2.2). As discussed in chapter 1, a 1:1 relative ratio of iodoform and ethylzinc iodide would lead to the I_2CHZnX carbenoid **1.42b**. With traces of water, or even with the labile proton of an alcohol, the species would be quenched to produce diiodomethane, inhibiting the cyclopropanation reaction (Figure 2.2, top). If I_2CHZnX carbenoid **1.42b** does not react immediately with the second equivalent of ethylzinc iodide, but rather with alkene **2.1'**, the resulting product is a mixture of *cis*- and *trans*-iodocyclopropane **2.4'**. The suite of mechanisms explains why the separate formation of the carbenoid and zinc alkoxide is required. If iodoform reacts completely with 2 equivalents of ethylzinc iodide to give $ICH(ZnX)_2$ carbenoid **2.2a**, subsequent cyclopropanation with alkene **2.1'** gives the *cis*-iodocyclopropane **2.3'** after iodide quench. In addition, the separate formation of the carbenoid and zinc alkoxide is required, as in the presence of a labile proton, $ICH(ZnX)_2$ carbenoid **2.2a** is quenched to produce the Simmons-Smith carbenoid **1.40**. Subsequent cyclopropanation with alkene **2.1'** gives the disubstituted dehalogenated cyclopropane **2.5'**. Alternatively, the Simmons-Smith carbenoid **1.40** can be converted into iodomethane in the presence of labile protons as well (Figure 2.2, top).

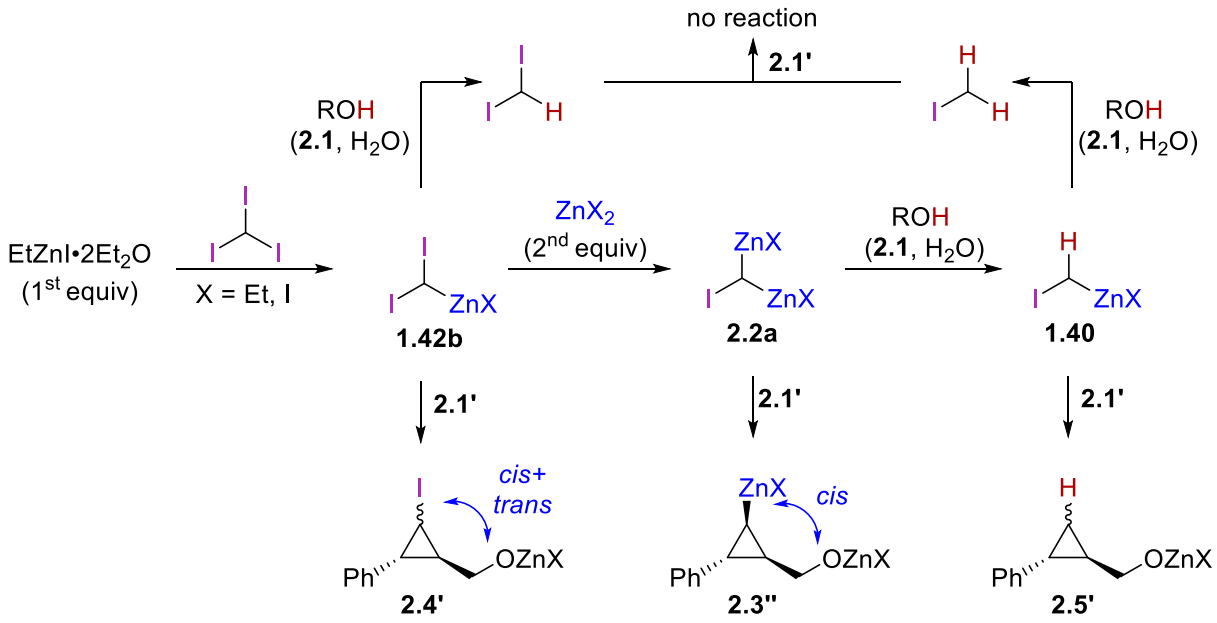


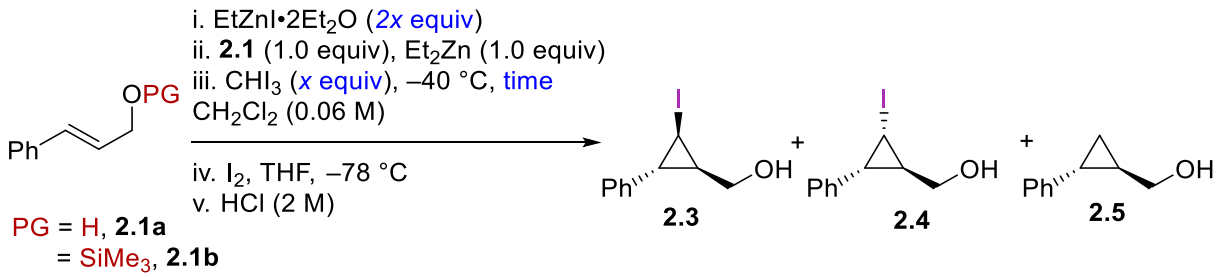
Figure 2.2 Origin of side product formation during carbenoid preparation.

2.1.2 Preliminary Zincocyclopropanation Results with Cinnamyl Alcohol

Initially, Zimmer's protocol was attempted on *trans*-cinnamyl alcohol **2.1a** using 2.2 equivalents of carbenoid **2.2a** (Table 2.1, entry 1). Unfortunately, no desired product **2.3** was observed and 12% of starting material **2.1a** was recovered along with 15% of *trans*-iodocyclopropane **2.4** and 39% of dehalogenated cyclopropane **2.5**. To drive the reaction to completion and to reduce the formation of side product **2.5**, the free alcohol in **2.1a** was protected with a trimethylsilyl group to prevent undesirable pathways where ROH would be involved (Figure 2.2). Starting with the same conditions, but using $SiMe_3$-protected **2.1b**, the desired *cis*-cyclopropane **2.3** was obtained in 42% along with 32% of starting material (Table 2.1, entry 2). To further push the reaction to completion, the stoichiometry of carbenoid **2.2a** was increased to 4.2 equivalents. Not only was the conversion still unsatisfactory, but undesired product **2.5** was still isolated in substantial quantities (entry 3). The reaction time was unsuccessfully reduced to 1 h (entry 4) and extended to 16 h to encourage completion of the reaction (entry 5). Unfortunately, none of the conditions provided desired *cis*-iodocyclopropane **2.3** in a satisfactory yield. Low yields are most likely due to the lack of reactivity between the alkene and the carbenoid, thus causing degradation of the carbenoid over time. Many drawbacks were associated with the reaction

conditions, including a complex procedure and large amounts of solvent due to the poor solubility of the iodoform and the high amount of diethyl zinc (Scheme 1.20).[83-86]

Table 2.1 Preliminary results of the zincocyclopropanation of *cis*-cinnamyl alcohol **2.1**.

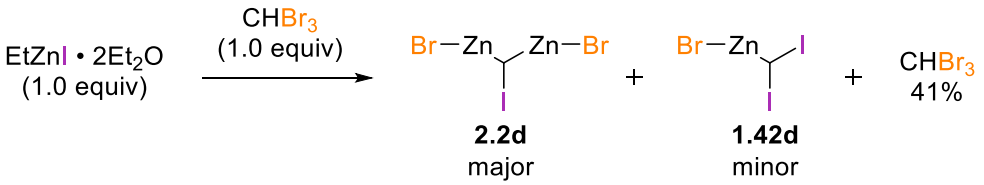


Entry	Substrate	Equiv of CHI_3 (*x*)	Time (h)	Yield			
				2.1(%)[a]	2.3 (%)[a]	2.4 (%)[a]	2.5 (%)[a]
1	**2.1a**	2.2	5	12	-	15	39
2	**2.1b**	2.2	5	32	42	-	21
3	**2.1b**	4.2	5	25	31	-	18
4	**2.1b**	2.2	1	39	15	-	25
5	**2.1b**	2.2	16	27	3	-	69

[a]Determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

2.1.3 Recent Dihalocarbenoid Studies

Recent comprehensive studies on hetero-dihalocarbenoids conducted by Dr. Taillemaud revealed that, unlike most haloform and ethylzinc halogen exchange, the combination of ethylzinc iodide and bromoform gives the *gem*-dizinc carbenoid $(XZn)_2CHI$ **2.2d** as the major product (Scheme 2.1).[122] Upon complete consumption of ethylzinc iodide dietherate, only traces of the monozinc carbenoid $XZnCHI_2$ **1.42d** were observed.



Scheme 2.1 Carbenoids formed from ethylzinc iodide dietherate and bromoform.

Surprisingly, despite the lack of C−I bonds in the starting material bromoform, iodomethane and traces of diiodomethane were observed after acid quenching of the carbenoid during carbenoid formation experiments.[122] The observation is consistent with the postulated double halide scrambling mechanism, which highlights the relative rates of halogen scrambling and reaction of zinc halides with carbenoid C−Br and C−I bonds (Figure 2.3). Mixing ethylzinc iodide and bromoform initially leads to the Br_2CHZnI species, that undergoes a fast halide scrambling to give BrICHZnBr. The intermediate can react with the second equivalent of ethylzinc iodide, by metathesis of the remaining C−I iodine with C−ZnI (major pathway) or by exchanging Zn−Br for Zn−I (secondary pathway). Upon scrambling and quenching of the two species, iodomethane was recovered from the *gem*-dizinc carbenoid **2.2d** and iodomethane was recovered from the monozinc carbenoid **1.42d**. The observation of iodomethane as the major product during carbenoid preparation experiments demonstrates that *gem*-dizinc species **2.2d** was formed almost exclusively under the conditions.

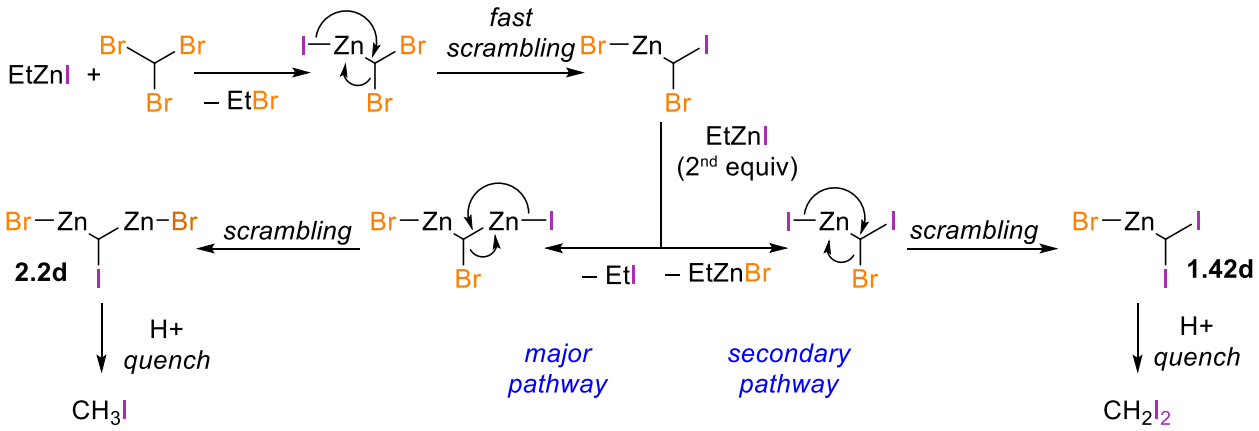


Figure 2.3 Double scrambling mechanism in zinc halocarbenoids.

2.2 Research Goals

Since ethylzinc iodide was completely consumed by only half of the bromoform when using a 1:1 ratio (Scheme 2.1), we postulated that increasing the relative ratio to 2:1 of EtZnI:$CHBr_3$ would lead to full consumption of bromoform (Figure 2.4). We sought to replace iodoform with bromoform as the source of carbenoid to proceed to zincocyclopropanation and obtain *cis*-iodocyclopropane **2.7** diastereoselectively. The strategy would streamline the synthesis of *cis*-iodocyclopropane by circumventing the poor solubility of iodoform in the reaction solvent.

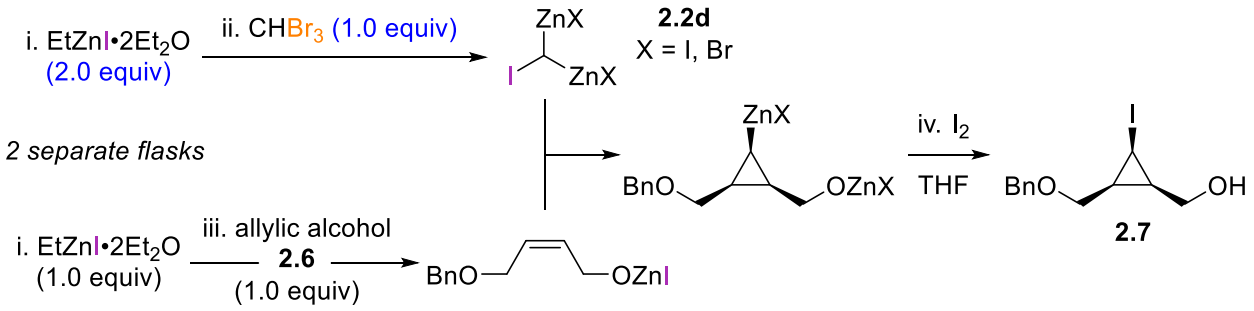
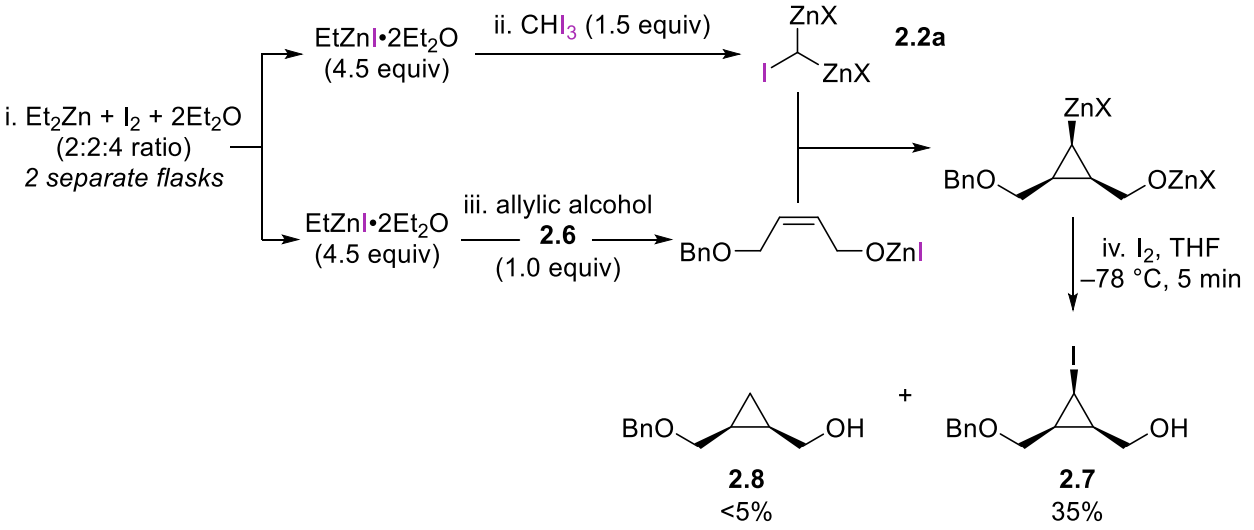


Figure 2.4 Suggested zincocyclopropanation with bromoform and allylic alcohol **2.6**.

2.3 Screening of Reaction Parameters

The initial protocol was based on a combination of previously published methods.[83-86] In Fournier's method, ethylzinc iodide was formed using diethyl zinc and iodine and the substrate **2.6** had two directing groups; a benzyl ether and zinc alkoxide (Scheme 2.2).[84] Since the alcohol must be deprotonated prior to carbenoid formation, the zinc alkoxide and carbenoid **2.2a** were prepared in two separate flasks. The zinc alkoxide was prepared from ethylzinc iodide etherate and not diethyl zinc to prevent undesired side reactions.

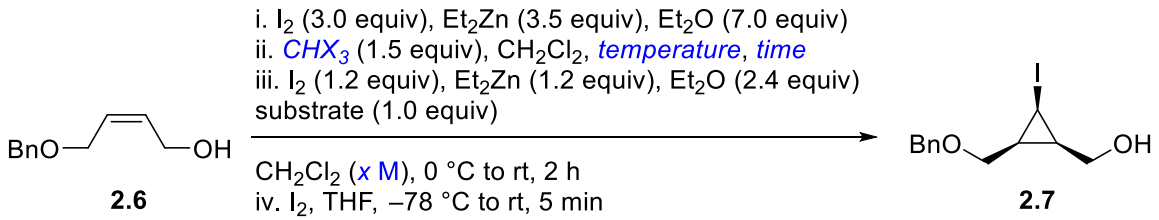


Scheme 2.2 Fournier's zincocyclopropanation protocol of allylic alcohol **2.6**.

Fournier's conditions were replicated and provided 35% of desired *cis*-iodocyclopropane **2.7** along with 42% starting material recovery (Table 2.2, entry 1). Our first modification was aimed at replacing iodoform with bromoform. Since bromoform is miscible in dichloromethane, the concentration of the reaction could be increased from 0.06 M with iodoform

to 0.16 M (entries 1 vs 2). Gratifyingly, a 69% yield of the desired cyclopropane **2.7** was obtained along with 21% of starting material **2.6** recovery (entry 2). It was hypothesized that the starting material recovery was caused by the instability of carbenoid **2.2d** that would degrade prior to the reaction. Therefore, to drive the reaction to completion and to prevent carbenoid degradation, the carbenoid formation temperature was decreased to 0 °C and the carbenoid formation time was reduced to 5 min (entries 3 and 4). The modifications resulted in lower yields for the desired cyclopropane **2.7**. The incorporation of bromoform as the carbenoid source seemed promising but further optimization was required. More importantly, only traces of **2.8** and no *trans*-iodocyclopropane were observed using the method.

Table 2.2 Preliminary results of cyclopropanation using bromoform and allylic alcohol **2.6**.



2.6 **2.7**

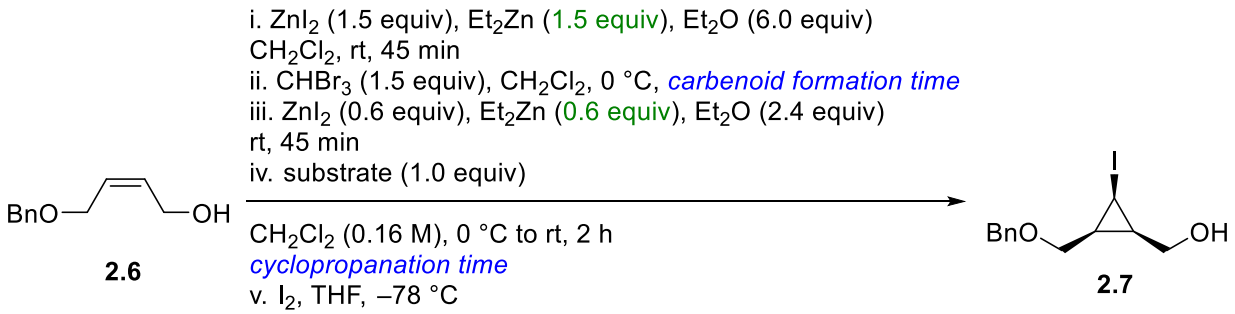
Entry	X	Carbenoid formation temperature	time (min)	Concentration (M)	Yield	
					2.6 (%)[a]	2.7 (%)[a]
1	I	rt	10	0.06	42	35
2	Br	rt	10	0.16	21	69
3	Br	0 °C	10	0.16	36	50
4	Br	0 °C	5	0.16	64	31

[a]Determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

Since the substitution of iodine for zinc iodide was previously fruitful,[18] we next examined conditions in which zinc iodide would be used as the ethylzinc iodide precursor. The substitution would allow reduction of the diethyl zinc stoichiometry from 4.7 to 2.1 equivalents. The formation of ethylzinc iodide using zinc iodide instead of iodine took around 45 minutes at room temperature. The reaction could easily be monitored as the initially heterogeneous reaction mixture turned into a colorless solution when the zinc iodide was fully consumed. Bromoform was then added to the homogenous ethylzinc iodide solution and the mixture was stirred at 0 °C for 10 min. The alkene was then added, and the mixture was stirred at room temperature for 2 h followed by the iodine

quench. Under the protocol, the desired iodocyclopropane was obtained in 50% yield along with 36% of remaining starting material (Table 2.3, entry 1). The cyclopropanation time was reduced to 30 minutes (entry 2) and extended one hour (entry 3), but lower yields were obtained. The carbenoid formation time was next studied and revealed that the carbenoid seemed to degrade over time, since a reduced yield of 30% of cyclopropane **2.7** was observed if the formation time was increased to 30 min (entries 4 and 5). However, with shorter or longer cyclopropanation times, starting material was still recovered. The significant amount of bromoform remaining in crude ^{1}H NMR led us to believe that the carbenoid formation or its stability was problematic (entries 3 to 5).

Table 2.3 Optimization of carbenoid formation and cyclopropanation times with allylic alcohol **2.6**.



Entry	Carbenoid formation time (min)	Cyclopropanation time (h)	Yield	
			2.6 (%)[a]	2.7 (%)[a]
1	10	2.0	36	50
2	10	0.5	89	7
3	10	1.0	35	43
4	5	2.0	40	43
5	30	2.0	53	30

[a]Determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

To better manage the high number of variables, the protocol was modified to be more user-friendly by combining the formation of ethylzinc iodide etherate, the zinc alkoxide, the carbenoid, and the cyclopropanation in a single flask (Figure 2.5). To the 4.5 equivalents of ethylzinc iodide etherate was added allylic alcohol **2.6**, which consumes 1.0 equivalent of ethylzinc iodide and gives zinc alkoxide intermediate **2.6'**. Upon the addition of bromoform, the remaining 3.5 equivalents of

ethylzinc iodide formed *gem*-dizinc carbenoid **2.2d**. The *in situ* generated carbenoid can cyclopropanate the zinc alkoxide **2.6'**, hopefully without any undesired degradation.

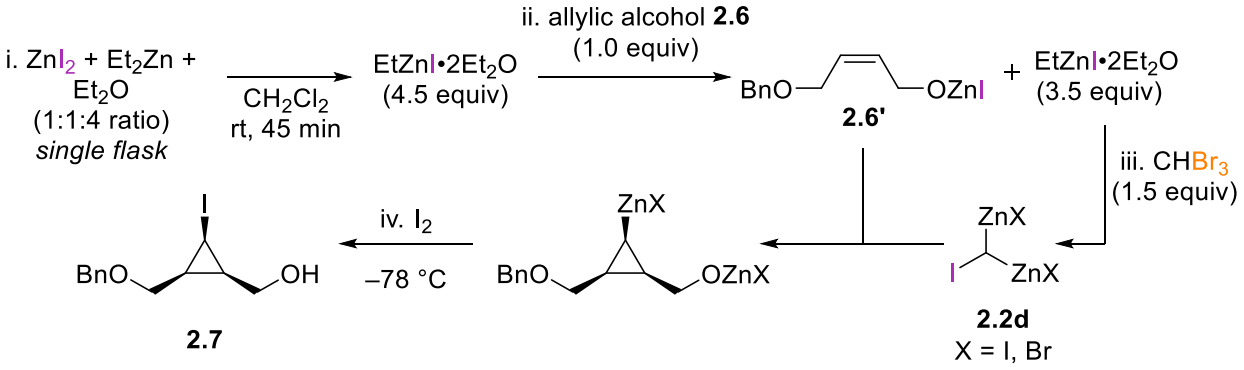
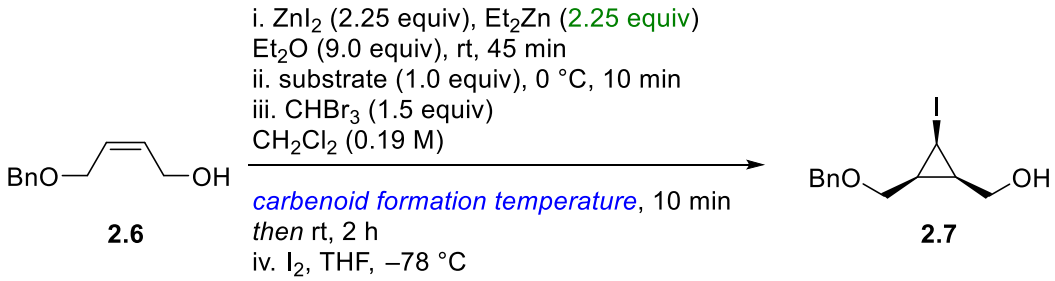


Figure 2.5 Improved zincocyclopropanation protocol of allylic alcohol 2.6.

Although the modified protocol gave similar results (Table 2.4, entry 1), it proved beneficial in allowing the use of a single reaction vessel. The reaction concentration could be increased from 0.16 M to 0.19 M. Using the new protocol, bromoform was still recovered in substantial amounts. The temperature at which the carbenoid was formed, was decreased to −40 °C, which provided 59% yield of desired product **2.7** along with a reduced amount of bromoform (entry 2). Since reactions with organozinc species tend to be exothermic, the formation of unequal heat during the bromoform addition could take place. As such, carbenoid **2.2d** degradation before the complete addition of bromoform could explain incompletion of the cyclopropanation reaction when the carbenoid was formed at 0 °C or −40 °C. The carbenoid formation temperature was further lowered to −78 °C, which allowed for complete consumption of both the starting material **2.6** and bromoform, and the formation of desired cyclopropane **2.7** in 86% yield (entry 3).

Table 2.4 Effect of carbenoid formation temperature for the zincocyclopropanation of allylic alcohol **2.6**.

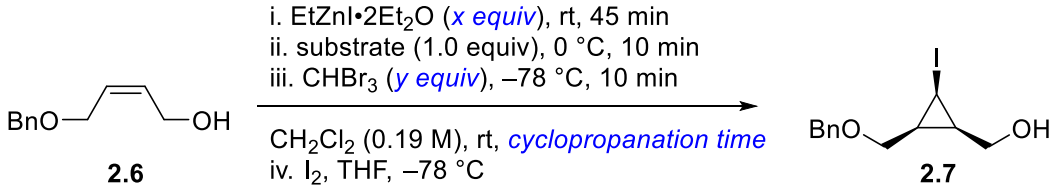


Entry	Carbenoid formation temperature (°C)	Yield		
		$CHBr_3$ (%)[a]	**2.6** (%)[a]	**2.7** (%)[a]
1	0	36	52	36
2	−40	19	41	59
3	−78	-	-	86

[a]Determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

The last parameter to study was the stoichiometry of the carbenoid. With 1.5 equivalents of carbenoid **2.2d**, 86% of *cis*-iodocyclopropane **2.7** was obtained (Table 2.5, entry 1). The relative ratio of ethylzinc iodide dietherate and bromoform must be at least 2:1 and 1.0 equivalent of ethylzinc iodide is mandatory for the alcohol deprotonation. Hence, the minimum amount of ethylzinc iodide is 3.0 equivalents, which can be formed from 1.5 equivalents of diethyl zinc and 1.5 equivalents of zinc iodide. Unfortunately, the cyclopropanation was incomplete under such reaction conditions (entry 2). Increasing the stoichiometry led to degradation of the zincocyclopropyl intermediate (entries 3 and 4). Lastly, the cyclopropanation time was reduced to reveal that the reaction requires at least one hour at room temperature to be completed (entries 5 and 6).

Table 2.5 Effect of EtZnI and carbenoid equivalents and reaction time for the zincocyclopropanation of allylic alcohol **2.6**.



2.6 **2.7**

Entry	Equivalents of		Cyclopropanation time (h)	Yield	
	EtZnI•2Et$_2$O (*x*)	**CHBr$_3$ (*y*)**		**2.6 (%)[a]**	**2.7 (%)[a]**
1	4.5	1.5	2.0	-	86
2	3.0	1.0	2.0	25	59
3	4.5	2.0	2.0	-	74
4	4.0	2.0	2.0	-	7
5	4.5	1.5	1.0	-	91
6	4.5	1.5	0.5	48	40

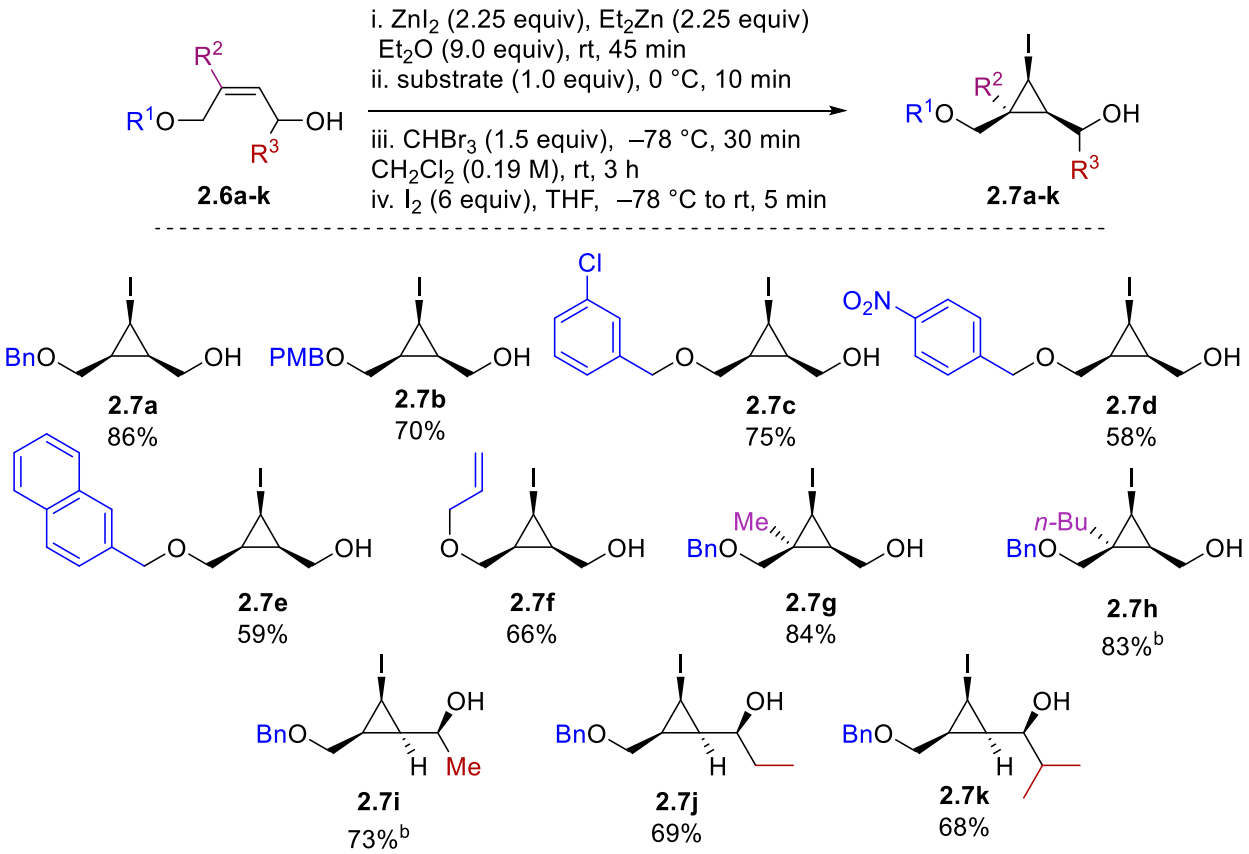
[a]Determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

2.4 Expanding the Substrate Scope of the Zincocyclopropanation

The optimized conditions were successfully applied to a variety of alkenes (Table 2.6). During the early elaboration of the scope, we realized that a reaction time of 3 h was necessary in most cases to ensure completion. Electron-rich arene such as *p*-methoxybenzyl (PMB) analog **2.7b** gave a 70% yield, whereas electron-poor aryl substituents such as *meta*-chlorobenzyl **2.7c** and *p*-nitrobenzyl **2.7d** gave 75% and 58% yields, respectively. 2-Naphthyl **2.7e** gave 59% yield. In the last two examples, the lower yields obtained were due to poor solubility of the alkene substrate. Interestingly, the arylmethyl substituent was not mandatory as the reaction proceeded selectively in the presence of an allyl group, providing **2.7f** in 66% yield. Trisubstituted alkenes were submitted to the cyclopropanation conditions. An excellent 84% yield was observed for the formation of cyclopropane **2.7g**, containing a methyl at the 2-position. Conversely, the cyclopropanation was incomplete after 3 h, with 1.5 equivalents of carbenoid, for the synthesis of cyclopropane **2.7h**, containing a butyl group. The issue was addressed by increasing the carbenoid to 2.0 equivalents to obtain product **2.7h** in 83% yield. Such conditions were used with secondary allylic alcohols, namely to produce methyl analog **2.7i** in 73% yield. Cyclopropanes **2.7j** and **2.7k**,

containing respectively an ethyl or an isopropyl substituent were produced in 69% and 68% yields respectively, using 1.5 equivalents of carbenoid. Unfortunately, increasing the stoichiometry of the carbenoid to 2.0 equivalents proved unsuccessful for **2.7j**, as only 18% yield of the desired product was observed. In all cases, no more than 5% of dehalogenated cyclopropane **2.8** and only one diastereomer of *cis*-iodocyclopropanes **2.7a-k** were observed. Except for **2.8d**, dehalogenated cyclopropanes **2.8-k** were easily separated from desired *cis*-iodocyclopropanes **2.7a-k** by flash chromatography. Compared to Fournier's method,[84] the reaction conditions are more user-friendly with a broader scope.

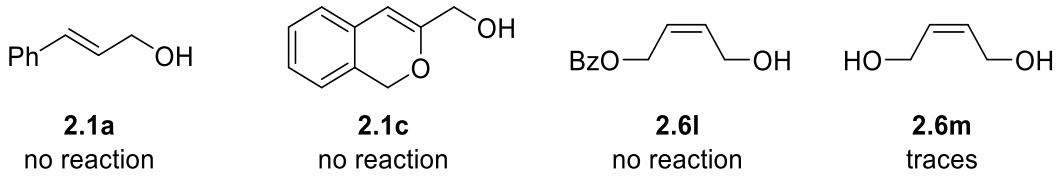
Table 2.6 Scope of *cis*-iodocyclopropanes formed under the developed zincocyclopropanation conditions.



[a]Isolated yields of single diastereomer on a 0.73 mmol scale. [b]2.0 equiv of bromoform and 5.2 equiv of $EtZnI•2Et_2O$.

Some substrates did not provide desired *cis*-iodocyclopropanes under the zincocyclo-propanation conditions. The removal of a directing group was completely detrimental to the

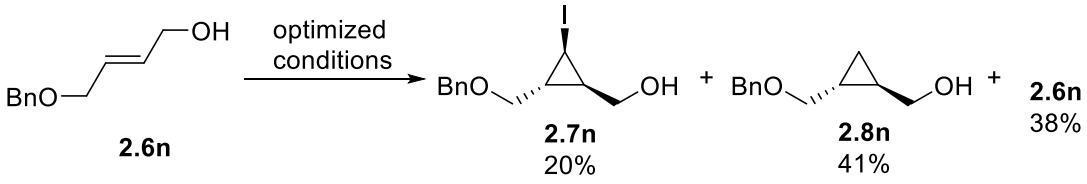
reaction. No reaction was observed for the zincocyclopropanation of cinnamyl alcohol **2.1a** (Figure 2.6). The configuration of oxygens in chromenol **2.1c** could not provide successful coordination in the transition state even with two coordinating groups. When the benzyl protecting group was replaced by a benzoyl group in **2.6l**, only starting material was recovered under zincocyclopropanation optimized conditions, most likely due to increased steric effects. Similarly, even with a supplementary equivalent of ethylzinc iodide, only traces of desired product and diiodomethane were observed for the 2-butene-1,4-diol **2.6m**, which lacks a benzyl protecting group.



2.1a no reaction | **2.1c** no reaction | **2.6l** no reaction | **2.6m** traces

Figure 2.6 Unsuccessful substrates for zincocyclopropanation.

(*E*)-4-(Benzyloxy)but-2-en-1-ol **2.6n** was submitted to zincocyclopropanation conditions (Scheme 2.3). Unfortunately, only 20% of desired *cis*-iodocyclopropane **2.7n**, along with 41% of dehalogenated cyclopropane **2.8n** were obtained. The poor result is most likely due to the inadequate configuration of the directing group (CH_2OBn in *trans*), which circumvents a second coordination in the transition state.



2.6n | **2.7n** 20% | **2.8n** 41% | **2.6n** 38%

Scheme 2.3 Zincocyclopropanation of (*E*)-4-(benzyloxy)but-2-en-1-ol.

To better understand the limitations of the method, a transition state was postulated and is depicted in Figure 2.7.[85] In the zincocyclopropanation, the removal of one oxygen eliminates a Zn−O coordination in the transition state, which is detrimental to the reaction.

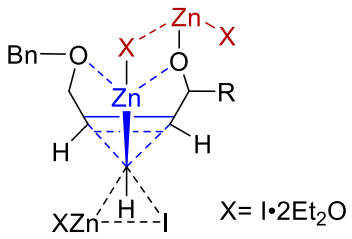


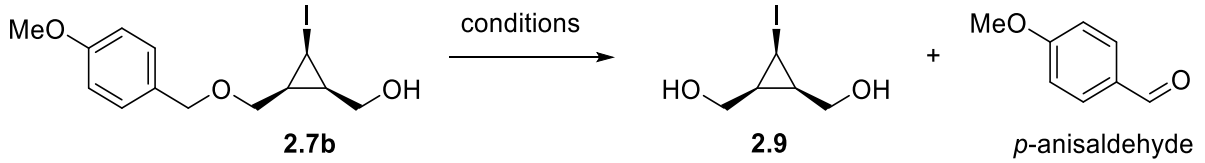
Figure 2.7 Zincocyclopropanation transition state.

2.5 Functionalization of *cis*-Iodocyclopropanes

To improve the scope of the reaction and the post-functionalization of the product cyclopropanes, the removal of the benzyl-protecting group was investigated. Due to lability of the C–I bond, removal of the benzyl ether is problematic under hydrogenolysis condition. Since the *p*-methoxybenzyl (PMB) protecting group is typically deprotected under milder conditions compared to a benzyl group, PMB-iodocyclopropane **2.7b** was submitted to various deprotection conditions (Table 2.7). To begin with, the most common oxidation conditions employing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were attempted (entry 1).[123] Although 73% of *p*-anisaldehyde side-product (which should be obtained in a 1:1 ratio with the deprotected cyclopropyl alcohol) was observed in the crude NMR spectrum, a low 16% yield of unprotected cyclopropane **2.9** was obtained. It was hypothesized that diol **2.9** was soluble in water and lost during the aqueous workup. Previously reported mild PMB deprotection conditions,[124] using 2.0 equivalents of tetrabromomethane in refluxing methanol, were attempted on substrate **2.7b** (entry 2). Some desired product was observed as the reaction was monitored by thin layer chromatography (TLC). However, even after addition of large excess of CBr_4, the reaction never went to completion and the product started to degrade after 48 hours. Recently developed aerobic photo-oxidation Eosin Y-catalyzed deprotection conditions were then investigated.[125] The deprotection conditions first lead to the oxidized benzyl alcohol, namely the corresponding benzoyl adduct, before the subsequent cleavage of the benzoyl group. Using the conditions, no reaction was observed for the deprotection of **2.7b** (entry 3). Lastly, deprotection methods using cerium reagents were attempted. Upon addition of cerium(IV) triflate hydrate (10 mol%) in refluxing nitromethane,[126] complete degradation was observed after 30 minutes (entry 4). Ceric ammonium nitrate ($Ce(NO_3)(NH_4)_2$, CAN) in wet acetonitrile provided deprotected cyclopropane **2.9** in 45% isolated yield after 30 minutes at room temperature (entry 5). Convenient and mild deprotection conditions using

cerium chloride heptahydrate and sodium iodide in refluxing acetonitrile without a subsequent aqueous extraction were developed.[127] Although the substrates previously deprotected under such conditions did not include cyclopropanes, alkyl iodides, nor free alcohols, the reaction conditions afforded the desired deprotected cyclopropane **2.9** in a 75% isolated yield after chromatographic separation (entry 6). Although satisfactory, it may be possible to further optimize the process to convert the remaining 15% starting material to **2.7b** recovered in the crude reaction mixture.

Table 2.7 Deprotection conditions on a PMB-protected cyclopropane.



2.7b **2.9** *p*-anisaldehyde

Entry	Conditions	Yield 2.9 (%)[a]
1	DDQ (1.2 equiv), CH_2Cl_2, rt, 16 h	16
2	CBr_4 (10.0 equiv), MeOH, reflux, 48 h	-
3	Eosin Y•TiO_2 (5 mol%), blue LEDs, acetone, rt, 14 h	-
4	$Ce(OTf)_3$•H_2O (10 mol%), $MeNO_2$, 100 °C, 30 min	-
5	CAN (3.5 equiv), CH_3CN/H_2O (40:1), rt, 30 min	45
6	$CeCl_3$•$7H_2O$ (1.5 equiv), NaI (1.0 equiv), CH_3CN, 82 °C, 24 h	75

[a]Isolated yield.

2.6 Conclusion

In conclusion, an improved and user-friendly zincocyclopropanation using bromoform was developed. Whereas previous zincocyclopropanation conditions involved a mixture of the monozinc $XZnCHX_2$ and *gem*-dizinc $(XZn)_2CHX$ carbenoids when using CHI_3 and EtZnI, *gem*-dizinc $(XZn)_2CHI$ carbenoid is exclusively obtained from $CHBr_3$ and EtZnI. The reaction concentration was increased by a 10-fold factor, streamlining the procedure by reducing the amount of required solvent and improving the efficiency of the reaction. Additionally, a cheaper source of zinc was used, as half of the previously required equivalents of Et_2Zn was replaced by ZnI_2. The newly developed reaction conditions expanded the scope of allylic alcohols that could be used in

the reaction. In all cases, *cis*-iodocyclopropanes were produced in high yields and diastereocontrol. An innovative application of *cis*-iodocyclopropanes will be presented in the next chapter.

2.7 Bibliography

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3. Synthesis of Electron-Rich 2-Substituted Bicyclo[1.1.0]butanes and Exploration of Their Potential as Building Blocks

3.1 Previous Work on the Synthesis of Bicyclo[1.1.0]butanes

Despite their well-established versatility as strain-release reagents (Section 1.2.3), the methods to prepare bicyclo[1.1.0]butanes (BCB) from inexpensive and readily available starting materials have drawbacks with regards to the nature and position of the substituents (Figure 3.1).[41,128-142] Approaches for the preparation of BCBs include the transannular ring closure, the cyclization of cyclopropyl lithium species, and the cyclopropanation of an unsaturated diazo compound or alkyne starting material.

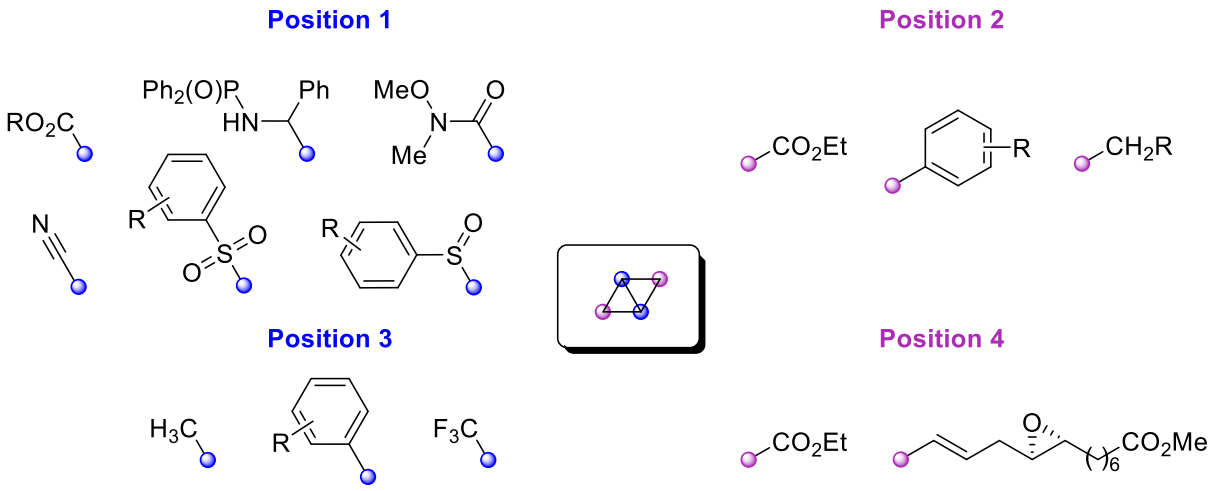
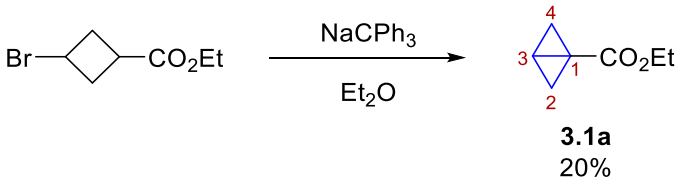


Figure 3.1 Currently accessible BCB substitution pattern

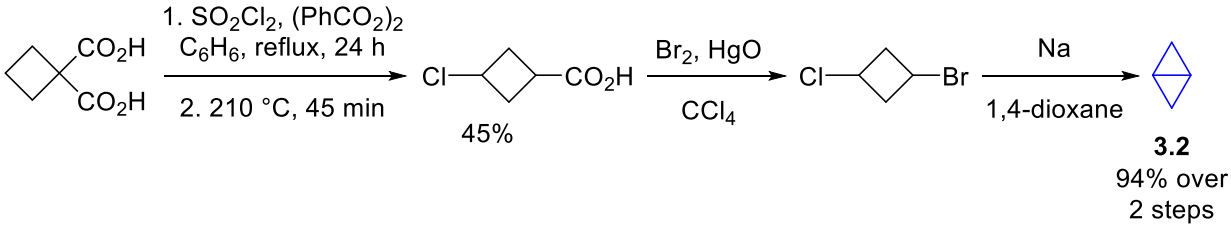
3.1.1 Transannular Ring Closure

Although the synthesis of a BCB was first reported in 1956 by Wiberg and Ciula,[128] it is only recently that interest in the derivatives has increased due to their potential use as bioisosteres ups for medicinal chemistry. In the original synthesis of the first BCB, ethyl 3-bromocyclobutane-l-carboxylate was submitted to a transannular ring closure under basic conditions to provide ethyl bicyclo[1.1.0]butane-1-carboxylate **3.1a** in a 20% yield (Scheme 3.1).



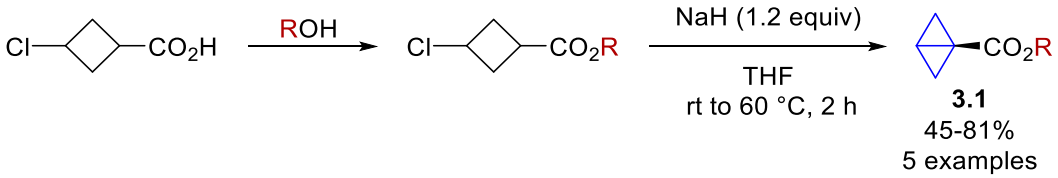
Scheme 3.1 Wiberg's pioneering synthesis of a BCB framework.

The parent structure, bicyclo[1.1.0]butane **3.2** itself, was not prepared until 1963 (Scheme 3.2).[129] A chloride leaving group was appropriately placed to undergo a Wurtz coupling, as the key step, providing the BCB skeleton. Although the 3-chlorocyclobutane carboxylic acid starting material was commercially available, it was synthesized from cyclobutane-1,1-dicarboxylic acid through a tandem free radical chlorination using sulfuryl chloride and subsequent thermal decarboxylation. The resulting 3-chlorocyclobutane-1-carboxylic acid underwent a mercury-derived Hunsdiecker reaction[130] to afford the 1-bromo-3-chlorocyclobutane as the starting material for the preparation of BCB **3.2**.



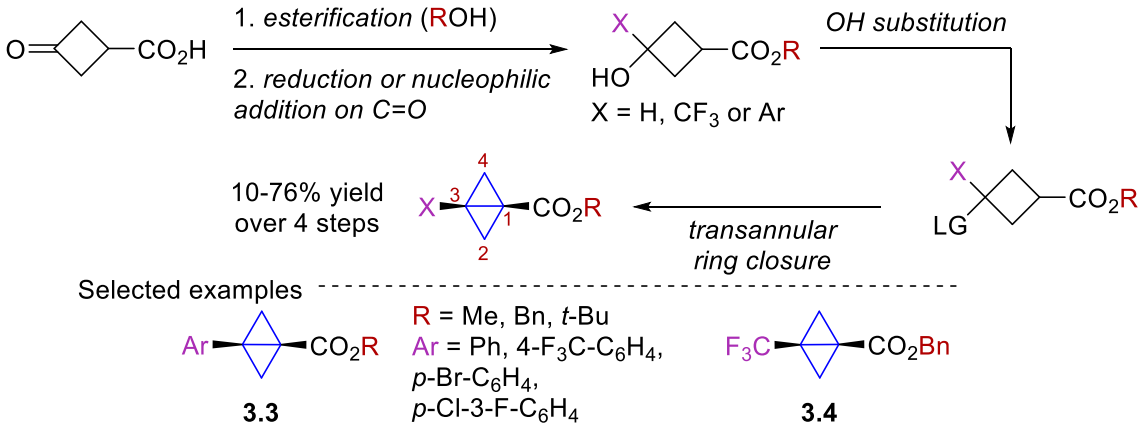
Scheme 3.2 First synthesis of an unsubstituted BCB.

A few years later, the transannular ring closure approach was applied to different BCB esters **3.1** (Scheme 3.3).[131] Wiberg's conditions were then later slightly improved.[132] 3-Chlorocyclobutane-1-carboxylic acid could be converted into its methyl, ethyl, isopropyl, 2,2,2-trifluoroethyl or phenyl esters under acidic conditions or through an acid chloride intermediate.[131] The transannular ring closure upon treatment of the ester with sodium hydride afforded BCBs **3.1** in good to excellent yields. The robust BCB syntheses were conducted on over 100 g scale and BCBs **3.1** could be kept at −40 °C for prolonged periods when in the presence of a radical inhibitor.



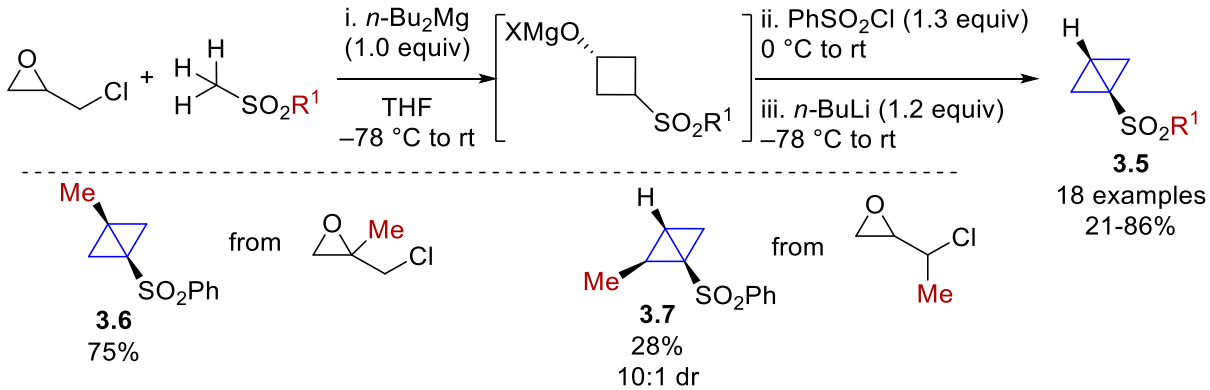
Scheme 3.3 Synthesis of BCB carboxylate esters.

The sequence could be modified to introduce substituents at the 3-position of the BCB framework.[47,50,133] First, the esterification of 3-oxocyclobutane-1-carboxylic acid was performed and nucleophilic addition afforded a disubstituted cyclobutanol (Scheme 3.4). The nucleophile could be a trifluoromethyl anion (from CsF/Me_3SiCF_3), an organomagnesium or an organolithium species. The subsequent conversion of the alcohol into a leaving group (LG), such as triflate or tosylate, followed by the key 3-*exo*-*tet* cyclization reaction using a strong base, such as potassium *t*-butoxide or potassium bis(trimethylsilyl)amide (KHMDS), provided the desired 1,3-disubstituted BCBs **3.3** and **3.4**. If the ketone was reduced to the alcohol instead of being substituted (step 2), BCBs **3.1** were obtained (Scheme 3.3).[133] Although the sequence is one step longer, the starting material 3-oxocyclobutane-1-carboxylic acid is substantially cheaper than the starting material 3-chlorocyclobutane-1-carboxylic acid. Starting from 3-oxocyclobutane-1-carbonitrile, BCB nitrile was obtained using the same method.[47] Although BCB esters were stable under chromatographic purification conditions,[50] it was observed that BCB esters and nitriles polymerized upon prolonged storage at 0 °C and were required to be stored under inert atmosphere at −30 °C.[47] Overall, the early introduction of the functional group resulted in stepwise syntheses and limited the applicability of the method. While substituents at the 3-position are dependent on the availability of a limited number of reagents such as organolithium species, organomagnesium species and cesium fluoride/(trifluoromethyl)trimethylsilane, substituents at the 1-position are limited to electron withdrawing groups, as the neighboring hydrogen must be acidic enough for subsequent deprotonation. Moreover, using cyclobutanes as starting materials is expensive and limited in terms of diversity.



Scheme 3.4 Syntheses of 1,3-disubstituted BCBs starting from oxocyclobutylcarboxylic acid.

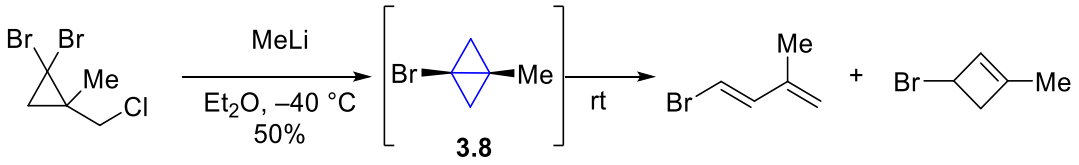
An alternative approach was developed in which an *in situ* generated four membered ring intermediate was generated from readily available methyl sulfones and inexpensive epichlorohydrins (Scheme 3.5).[134] Lindsay has previously observed BCB by-products when sulfone anions were treated with epichlorohydrins. Further optimization led to the use of commercially available dialkylmagnesiums, which can undergo sequential deprotonation leading to magnesium alkoxide bearing cyclobutylsulfones. The method successfully produced the largest scope of BCBs yet and introduced substitution at the 2-position to provide BCBs **3.5-3.7**. Moderate to excellent yields were obtained for various sulfone R^1 substituents (**3.5**) and 1,3-disubsituted BCBs **3.6**, and a significantly reduced yield (28%) was obtained for 1,2-disubsituted BCB **3.7**, albeit in good diastereoselectivity. The transformation could be performed on a gram scale with similar efficiency.



Scheme 3.5 Transannular ring closure of sulfonyl cyclobutanes to afford BCBs.

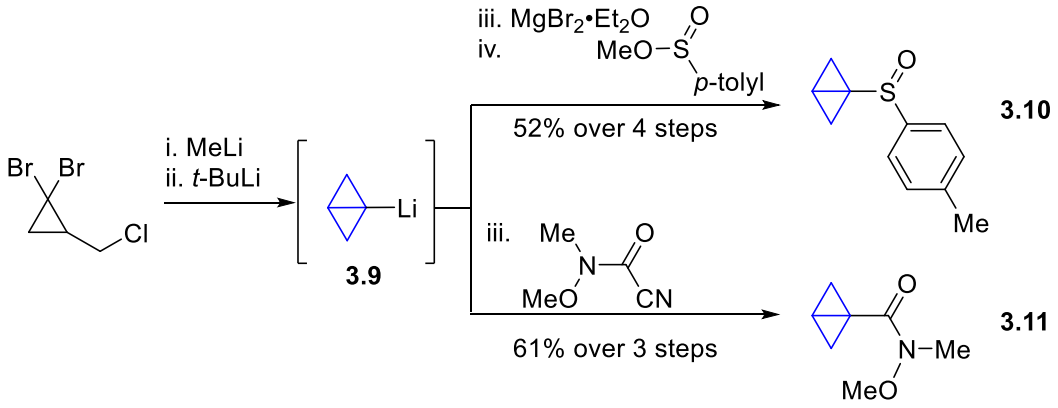
3.1.2 Cyclization of an Unstabilized Cyclopropyl Lithium Species

The second type of BCB synthesis, involving the cyclization of an unstabilized cyclopropyl lithium, was first reported by Skattebøl in 1984.[135] Upon 3-*exo-tet* cyclization of a (chloromethyl)cyclopropyl lithium species, 1-bromo-3-methyl-BCB **3.8** was observed at −40 °C as a single major product (Scheme 3.6). However, at room temperature, only butadiene isomers were observed, which supports the general observation that electron-rich BCBs are unstable under the above reaction conditions. Based on the stereochemistry of the recovered starting material, the *cis* relationship between the C–Li bond and the leaving group was necessary for the displacement to occur.



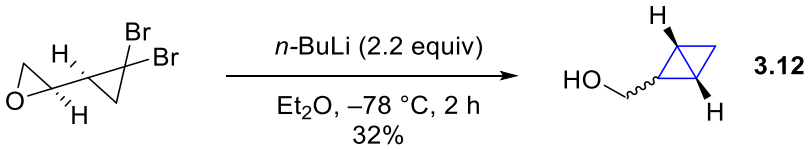
Scheme 3.6 BCB synthesis via cyclization of 1,1-dibromo-2-(chloromethyl)cyclopropane.

Slight modifications of the above method allowed for the synthesis of BCB ester **3.1**.[136] The replacement of MeLi with *t*-BuLi provided a bicyclo[1.1.0]butyl lithium species intermediate that was quenched with ethyl chloroformate. Although the method has been used by several groups,[41] it took over 35 years before it was significantly improved to allow the isolation of a synthetically useful and stable BCB. Intermediate **3.9** was submitted to a transmetalation upon treatment with ethyl magnesium bromide etherate and trapped with a sulfinate ester according to Skattebøl's conditions (Scheme 3.7, top).[57] The bench-stable bicyclo[1.1.0]butyl sulfoxide **3.10** was produced in 52% yield on a gram-scale. The conditions were applied to generate bicyclo[1.1.0]butyl amide **3.11** (Scheme 3.7, bottom),[137] that was used as a protein bioconjugation tool (Figure 1.6). BCB sulfones and amides were bench stable and could be stored under air at 0 °C.[47]



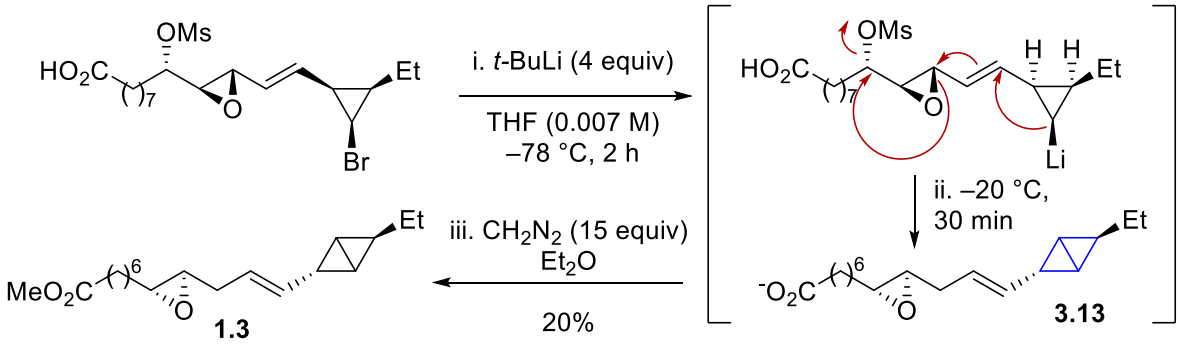
Scheme 3.7 Cyclization of 1,1-dibromo-2-(chloromethyl)cyclopropane for the synthesis of BCBs.

In 2005, the cyclopropyl lithium species strategy was employed in an addition reaction to a dibromocyclopropyl epoxide to provide the first 2-substituted BCB **3.12** (Scheme 3.8).[138] Unfortunately, only one example was reported in a poor 32% yield under the reaction conditions.



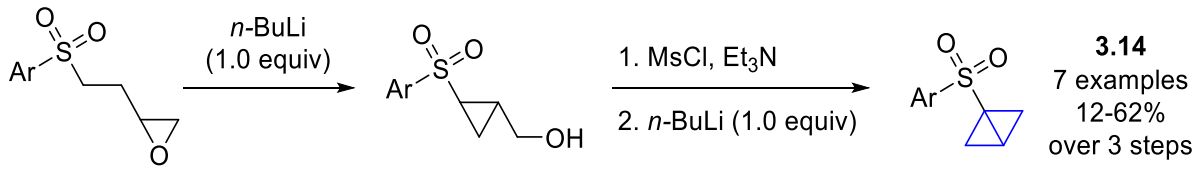
Scheme 3.8 Reductive cyclization of a bromocyclopropyl epoxide for the synthesis of a 2-substituted BCB.

The intramolecular 3-*exo*-*tet* cyclization of a cyclopropyl lithium was used in the total synthesis of BCB fatty acid **1.3**.[139] A cyclization/epoxide opening sequence, in a very low concentration to prevent intermolecular reactions, resulted in formation of BCB **3.13**. A subsequent methylation afforded the natural product **1.3** in a one-pot procedure and in 20% overall yield from the bromocyclopropane (Scheme 3.9). During the development of the synthesis, it was observed that any attempt to purify BCB **1.3** by chromatography or any of its structurally related analogs led to decomposition. A solution of BCB **1.3** in [D6]DMSO has an estimated half-life of 3 days.



Scheme 3.9 Cyclization and epoxide opening sequence toward a 2,4-disubstituted BCB fatty acid.

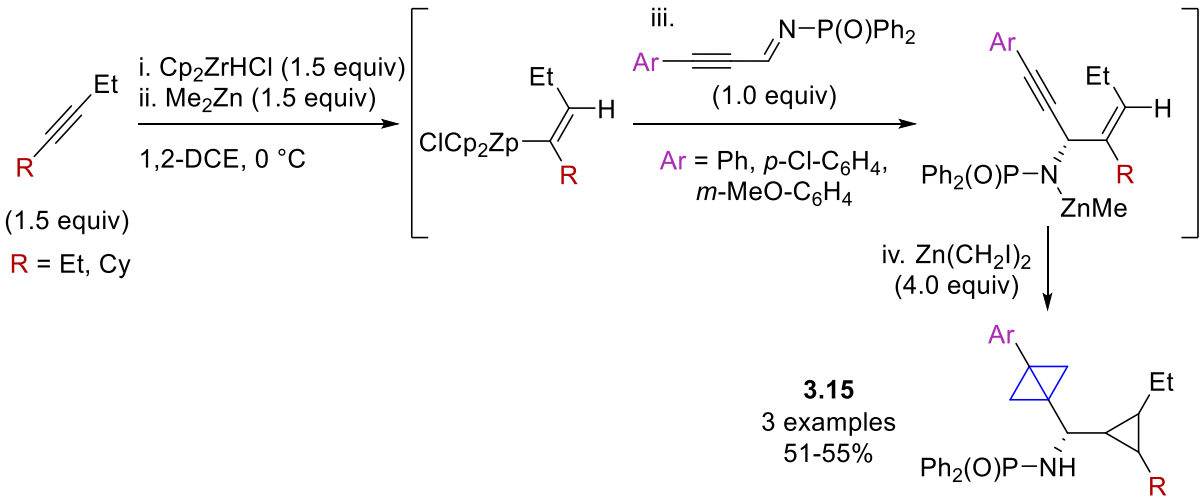
Similarly, Baran described a 6-step protocol to prepare 1-arylsulfonyl-BCBs **3.14** (Scheme 3.10).[44] Although the method was scalable, overall yields from commercial arylsulfonyl chlorides and 4-bromobut-1-ene were poor to good.



Scheme 3.10 Stepwise epoxide opening and cyclization toward stable BCB sulfones.

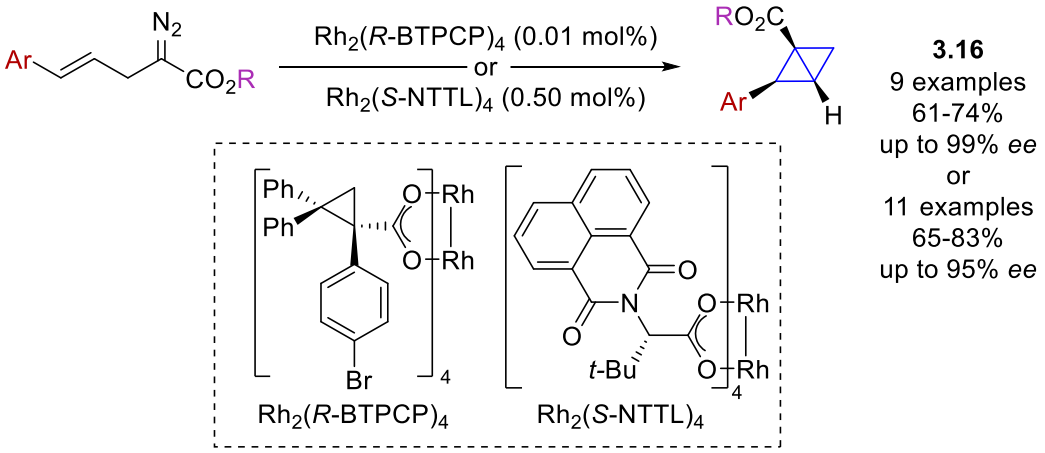
3.1.3 Intramolecular Double Cyclopropanation

The last approach to BCBs is the cyclopropanation of an unsaturated starting material that will undergo double cyclopropanation reactions to produce the BCB scaffold. Using a Wittig-Denmark carbenoid **1.35** (Figure 1.13), a hydrozirconation/transmetalation/imine addition/ cyclopropanation sequence reaction of an internal alkyne and an alkynyl imine led to triple cyclopropanation and afforded BCBs **3.15** (Scheme 3.11).[140] Unfortunately, modest yields and low functional group tolerance precludes a broader application of the reaction conditions.



Scheme 3.11 Double cyclopropanation on propargyl phosphoryl amines for the synthesis of 1,3-disubstituted BCBs.

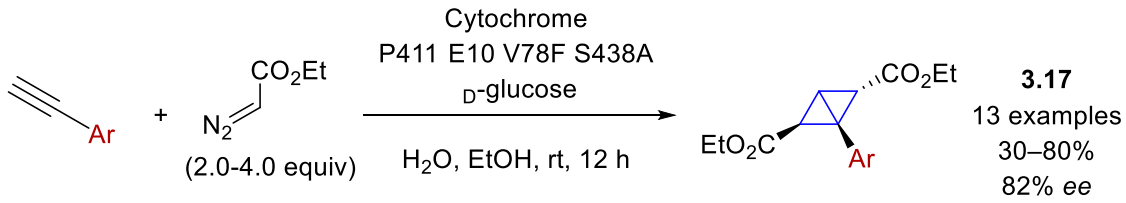
In 2013, Davies and Fox independently reported the synthesis of enantiomerically enriched and highly substituted BCB carboxylates **3.16** (Scheme 3.12).[42,141] The asymmetric rhodium(II)-catalyzed decomposition of diazo compounds allowed the enantioselective intramolecular cyclopropanation of (*E*)-2-diazo-5-aryl pent-4-enoates. The method was limited to semi- and stabilized diazo compounds due to the challenging synthesis of the requisite diazo compounds.



Scheme 3.12 Rhodium-catalyzed decomposition of diazo compounds toward 1,2-disubstituted BCBs.

Diazo compounds were involved in the synthesis of BCBs using biocatalysis as well. The enzymatic biocatalyzed decomposition of ethyl diazoacetate developed by Arnold provided 1,2,4-

trisubstituted BCBs **3.17** in up to 80% yield and 82% enantiomeric excess (Scheme 3.13).[142] The hemeprotein enzyme used for the transformation is in the cytochrome P450 family. Under the mild anaerobic conditions, the diazo compound substrate was limited to ethyl diazoacetate. Although the two double cyclopropanations mentioned would seem as the most efficient strategy, they either requires complex starting materials or are limited in the nature of the diazo compound.



Scheme 3.13 Enzymatic decomposition of ethyl diazoacetate to afford 1,2,4-trisubstituted BCBs.

3.2 Research Goals

The increasing interest towards the preparation of cyclobutanes for applications in medicinal chemistry has led to further method developments to access BCBs. As highlighted in section 1.2.3, BCBs can undergo a variety of novel functionalization reactions that further emphasizes the utility of the motif as a precursor to complex cyclobutanes.

All the previous BCB syntheses remain challenging and limited to having electron-withdrawing groups and/or bridge-head position substituents.[41,143] Typically, less-substituted and electron-rich BCBs are less stable than their 1,3-disubstituted sterically shielded, and electron-poor derivatives. Exploration of their reactivity is limited to the BCBs obtained by the known methods, leaving many areas of underexplored reactivity. Though the strength of the bridge bond dominates their reactivity, it is influenced by its substitution pattern and polarization as well. As mentioned by Fawcett; *"many areas of underexplored reactivity […] will be expedited by the development of convenient sources of nucleophilic BCB. These new reagents, hint at a much broader range of BCB-containing structures whose chemistry has yet to be evaluated."*[41b]

To overcome the dearth of methods to produce 2-substituted electron-rich BCBs, we proposed a two-step synthesis from *cis*-iodocyclopropanes **2.7**, involving a substitution of the alcohol by a leaving group followed by cyclization (Figure 3.2). For the last step to work, the iodocyclopropyl-methanol intermediate **3.18-3.21** required a *cis* relationship between the iodine and the alcohol chain, as highlighted by Skattebøl.[135] The second goal of this project was to study

the reactivity of the resulting compounds, as the method produced various electronically different BCBs (**3.22**).

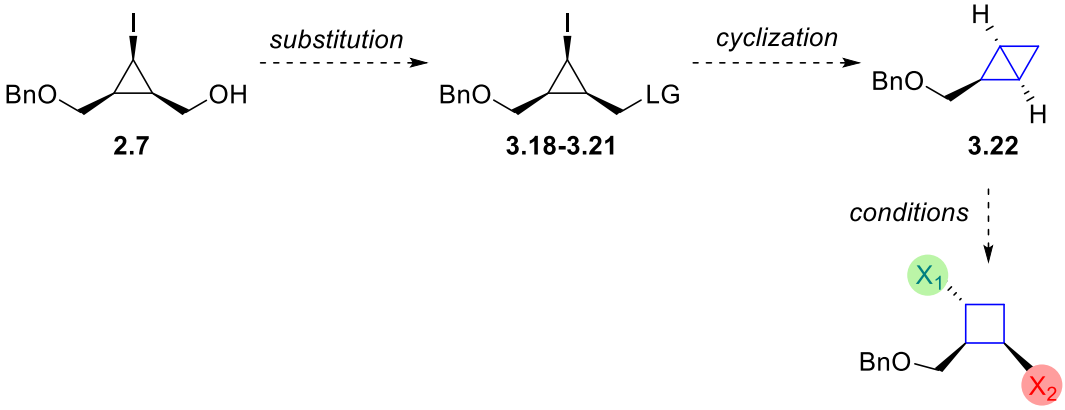


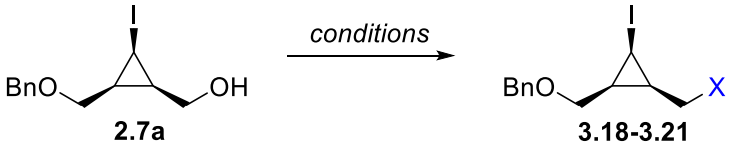
Figure 3.2 Proposed synthesis of 2-substituted electron rich bicyclo[1.1.0]butanes.

3.3 Screening of Reaction Parameters of the Intramolecular Ring Closure Reaction

The first step of the suggested sequence was the conversion of the alcohol of cyclopropane **2.7a** into a leaving group (Table 3.1). The initial strategy involved conversion of the alcohol into a halide. Although full conversion of the starting material **2.7a** was observed after treatment with triphenylphosphine and hexachloroacetone, the desired chloride **3.18** could not be separated from residual hexachloroacetone (Table, entry 1). Different halogenation conditions, such as Appel chlorination and bromination[144] were attempted (entries 2 and 3). Although 27% yield of the corresponding desired chlorinated cyclopropane **3.18** was observed, the reaction was still incomplete after 24 h under Appel chlorination conditions (entry 2). A poor yield of cyclopropane **3.19** was observed under Appel bromination conditions as well (entry 3). Bromination conditions of cyclopropylmethanol developed by Julie Naud, a former M. Sc. Charette group member, used a mesylate as the intermediate, followed by a halogen-mesylate displacement using *n*-tetrabutylammonium bromide (TBAB) as the bromide source.[145] When the conditions were applied to iodocyclopropane **2.7a**, no corresponding 1-(bromomethyl)-2-iodocyclopropane **3.19** was observed (entry 4). While the exploration for the conversion of cyclopropane **2.7a** into cyclopropanes **3.18** and **3.19** was not further studied, halogenation conditions could be potentially optimized (entries 2 and 3). The reaction was repeated to isolate mesylate **3.20** in quantitative yield

(entry 5). Additionally, (iodocyclopropyl)methanol **2.7a** was converted into the corresponding tosylate **3.21** (entry 6).

Table 3.1 Conversion of the alcohol of cyclopropane **2.7a** to a leaving group.



2.7a **3.18-3.21**

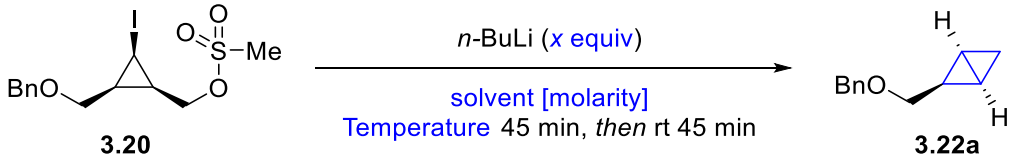
Entry	X	Conditions	Temp.	Time	Compound	Yield (%)[a]
1	Cl	PPh_3, hexachloroacetone	rt	3 h	**3.18**	-
2	Cl	PPh_3, CCl_4	rt	24 h	**3.18**	27
3	Br	Br_2, PPh_3, CH_2Cl_2	–40 °C to rt	3 h	**3.19**	13
4	Br	MsCl, TBAB, CH_2Cl_2	40 °C	10 h	**3.19**	-
5	OMs	MsCl, Et_3N, CH_2Cl_2	0 °C	30 min	**3.20**	99[b]
6	OTs	TsCl, pyridine, DMAP, CH_2Cl_2	0 °C	12 h	**3.21**	99[b]

[a]Isolated yield after chromatographic purification. [b]Isolated yield of the crude mixture after aqueous extraction and without purification.

Crude mesylate adduct **3.20** was submitted to *n*-BuLi using Bentley's conditions,[138] namely 2.2 equivalents of *n*-BuLi in diethyl ether (0.05 M) (Table 3.2, entry 1). Fortunately, a clean but volatile 2-substituted bicyclo[1.1.0]butane **3.22a** was obtained on the first trial. Any attempt to purify BCB **3.22a** by flash chromatography led to degradation, as observed with previous 2-subsituted BCBs.[139] THF was used as the solvent to obtain an increased crude 91% yield of BCB **3.22a** (entry 2). When fewer equivalents (1.1 or 1.5 equivalents) or excess (3.3 equivalents) of *n*-BuLi were used, lower yields were obtained, and starting material was recovered in the first two attempts (entries 3-5). While decreasing the reaction concentration to 0.01 M did not affect the yield significantly (entry 6), increasing the reaction concentration to 0.20 M led to the formation of trace amounts of a side product (entry 7). Although the compound was not isolated, it was hypothesized to be the result of an intermolecular displacement reaction to produce a dimer of **3.20** based on the ^{1}H NMR signals. Increasing the temperature at which *n*-BuLi was added, or the replacement of *n*-BuLi with *t*-BuLi, resulted in lower yields of BCB **3.22a** (entries 8 and 9). Scaling

up the reaction of cyclopropane **3.20a** to BCB **3.22a** on 10 mmol scale produced an excellent 90% yield, as long as the rate of addition of *n*-BuLi was limited to 5 mL/h to keep an internal reaction temperature below –70 °C (entry 10). It was concluded that using 2.2 equivalents of *n*-BuLi added at –78 °C and THF as the solvent at 0.05 M reaction concentration, was optimal and supplied BCB **3.22a** as a single diastereomer in an unpurified 91% yield (entry 2). The intramolecular cyclization of (iodocyclopropylmethyl)tosylate **3.21**, provided by Table 3.1, entry 7, gave BCB **3.22a** in a lower 40% under optimized conditions.

Table 3.2 Optimization studies for the cyclization of iodocyclopropyl mesylate **3.20**.



Entry	Equivalents of *n*-BuLi (*x*)	Solvent	Concentration (M)	Temperature (°C)	Yield 3.22a (%)[a]
1	2.2	Et_2O	0.05	–78	58
2	2.2	THF	0.05	–78	91 (38)[b]
3	1.1	THF	0.05	–78	44
4	1.5	THF	0.05	–78	68
5	3.3	THF	0.05	–78	72
6	2.2	THF	0.01	–78	84
7	2.2	THF	0.20	–78	74
8	2.2	THF	0.05	–40	74
9[c]	2.2	THF	0.05	–78	42
10[d]	2.2	THF	0.05	–78	90

[a]Determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. Entries done on 0.25 mmol. [b]Isolated yield shown in parentheses. [c]Entry done using *t*-BuLi instead of *n*-BuLi. [d]10 mmol scale

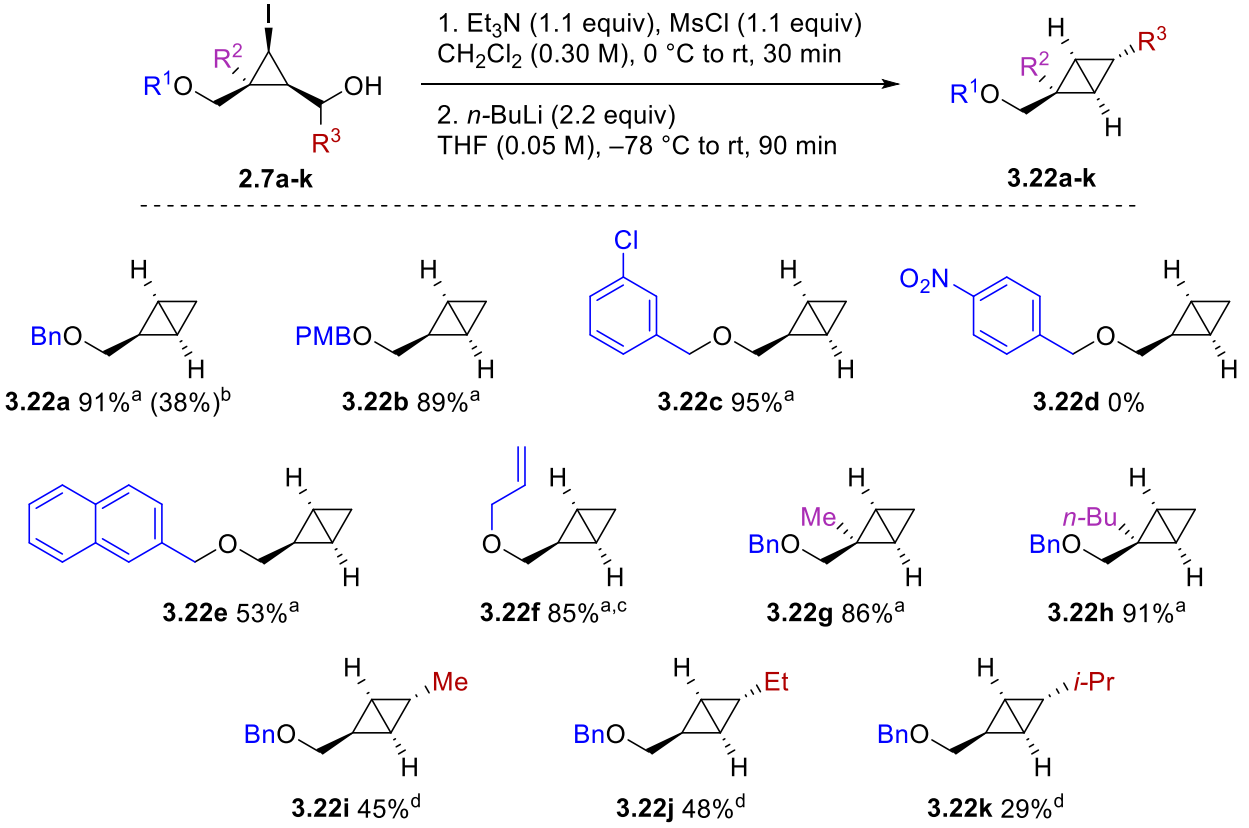
The resulting BCB **3.22a** could be treated with sodium bicarbonate during the aqueous workup, extracted using diethyl ether as the extraction solvent, and dried using magnesium sulfate as the drying agent. As BCB **3.22a** has a low boiling point, THF evaporation must be meticulous,

and the post-functionalization reactions were often carried out with traces of remaining THF. While it was unnecessary to purify BCB **3.22a** as the cyclization was very clean and no side products were observed, any chromatographic attempt to purify **3.22a** over silica, including the use of triethylamine-deactivated silica, failed.

3.4 Expanding the Substrate Scope of the Intramolecular Ring Closure Reaction

The scope of the reaction of the intramolecular ring closure reaction was expanded under the optimized reaction conditions (Table 3.3). Upon the intramolecular ring closure reaction of cyclopropane **2.7a**, BCB **3.22a** was obtained in 91% yield. Since any attempt to purify BCB **3.22a** by flash chromatography led to degradation and that no side product was observed, BCB **3.22a–k** yields are reported without purification and over two steps from **2.7a–k**. The transformation proceeded smoothly and in moderate to good yields with various substituted benzyl and allyl substituents. A *p*-methoxybenzyl ether substituent gave BCB **3.22b** in 89% yield. The cyclization tolerated electron-poor benzyl ethers as **3.22c** could be prepared in an 95% yield. Unfortunately, only degradation and no desired BCB **3.22d** was observed with the *p*-nitrobenzyl derivative. When the benzyl group was replaced with a 2-naphthylmethyl group, only 53% of BCB **3.22e** was obtained, due to starting material solubility issues. When the benzyl ether was replaced with an allyl ether, BCB **3.22f** was not isolated because of its low boiling point. The cyclization was conducted in diethyl ether as the reaction solvent, instead of tetrahydrofuran, and **3.22f** was obtained in solution. Lower yield of BCB **3.22a** (58% yield) was also observed when the cyclization was carried out in diethyl ether as the solvent (Table 3.2, entry 1). The cyclization provided 2,2-disubstituted BCBs **3.22g–h** with yields of 86% and 91% respectively (Table 3.3). Due to their high volatility and instability on silica, BCBs **3.22a-h** yields were reported from crude NMR from unpurified reaction mixture after aqueous extraction. The reaction tolerated substitution on tertiary carbons with decreased yields as the carbon bearing the leaving group during the ring-closing step is more hindered. Entries with methyl, ethyl as well as isopropyl substituents **3.22i–k** were synthesized in moderate yields. Due to the formation of side products, BCBs **3.22i–k** NMR yields were reported using triphenylmethane as the internal standard. Neat BCBs **3.22i–k** were particularly unstable after workup. The herein-developed method afforded 10 examples of 2-, 2,2- and 2,4-substituted BCB derivatives in 29 to 95% yields.

Table 3.3 Scope of electron rich 2-substituted bicyclo[1.1.0]butanes prepared by the cyclization method.



[a]Yield determined by ^{1}H NMR spectroscopy of crude reaction mixtures after aqueous extraction and without purification. [b]Yield after purification over silica gel. [c]Using diethyl ether instead of THF as the reaction solvent. [d]Yield determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

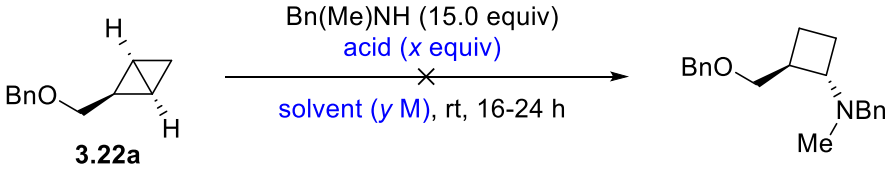
The cyclization method to afford BCBs is the only method that provides *trans*-2-ethyl-4-substituted BCB with no substituent at C1, as in the natural product **1.3** (Figure 1.1, Scheme 3.9). Due to their high volatility and instability on silica, BCBs **3.22a-k** were characterized as their ring opened corresponding products (Scheme 3.14, Tables 3.4-3.5).

3.5 Functionalization of 2-Substituted Electron-Rich BCBs

To explore the synthetic utility of electron rich BCBs, BCB **3.22a** was investigated in several post-functionalization reactions. BCB **3.22a** was exposed to various nucleophiles starting with Baran's cyclobutylation conditions, albeit slightly modified without lithium chloride due to

the removal of the sulfone functional group (Table 3.4, entry 1).[44] Under the conditions, BCB **3.22a** did not provide the corresponding cyclobutylamine and the starting material was fully recovered. BCB **3.22a** was combined with a large excess of *N*-methylbenzylamine to accelerate the reaction (entry 2). Pyridinium *p*-toluenesulfonate (PPTS) and LiCl or HCl were also studied as additives to promote the ring-opening reactivity of BCB **3.22a** (entries 3 and 4). Unfortunately, in all cases, only BCB **3.22a** was recovered.

Table 3.4 Nucleophilic addition of amines on electron rich 2-substituted BCB **3.22a**.



Entry	Aci	Equiv of acid (*x*)	Solvent	Concentration (M)
1	-	-	DMSO	0.4
2	-	-	-	-
3[a]	PPTS	2.5	-	-
4	HCl	15.0	-	-

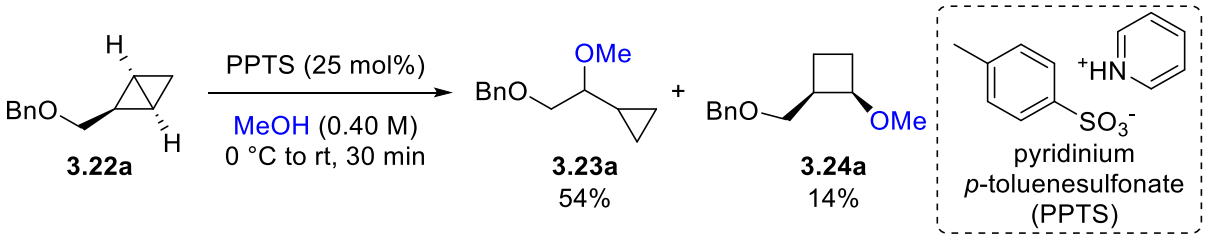
[a]LiCl (3.0 equiv) was added.

BCB **3.22a** was submitted to various reaction conditions using benzylamine or benzylamine hydrochloride. In all cases, no desired cyclobutylamine was observed. Upon various nucleophilic and basic conditions, such as sodium methoxide, diverse amines, pinacol and catechol boranes, BCB **3.22a** showed high stability and only starting material was recovered.

3.5.1 Reactivity of Electron Rich 2-Substituted BCBs under Acidic Conditions

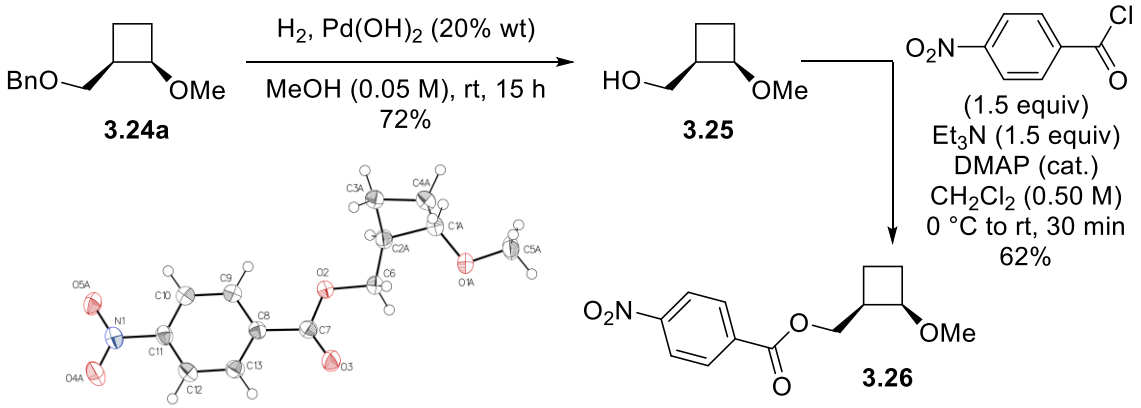
Since BCB **3.22a** was unreactive towards bases, its reactivity under acidic conditions was explored next. The acid sensitivity of BCB **3.22a** was observed under silica gel chromatographic purification. When BCB **3.22a** was treated with PPTS (pK_a = 5.2) in methanol, a mixture of cyclopropane **3.23a** and cyclobutane **3.24a** were obtained in a 3.8:1 ratio, in 68% overall yield (Scheme 3.14). Considering that the conversion of BCB **3.22a** into cyclobutane **3.24a** is interesting and potentially useful, many conditions were tested to improve the yield. Numerous Brønsted-Lowry acids of various acidities, such as H_2SO_4, TFA, Ph_2PO_4H and AcOH, and the Lewis acid

$AlCl_3$ were tested for the transformation. Unless the pK_a of the acid was higher than 6.8, such as in $TfNH_2$, KH_2PO_4 and K_2HPO_4, less than 10% conversion was observed. The yield was similar (55-65%) in all cases. The effect of the temperature and the time were studied as well. The ratio of products did not vary with temperature or time. Only the cyclobutane isomer **3.24a** was observed in the acid-catalyzed ring opening reaction.



Scheme 3.14 Methanol addition to an electron rich 2-substituted BCB catalyzed by PPTS.

To confirm its stereochemistry, cyclobutane **3.24a** was converted into one derivative that could be recrystallized and analyzed by X-ray crystallography. Upon hydrogenolysis, cyclobutylmethanol **3.25** was obtained in a 72% isolated yield (Scheme 3.15). The subsequent esterification to install *p*-nitro-benzoate was completed in a 62% isolated yield. After several weeks, a solution of cyclobutane **3.26** in diethyl ether and hexanes led to the formation of crystals that were suitable for X-ray crystallography and revealed a *cis* configuration.



Scheme 3.15 Derivatization of cyclobutane for crystallization.

To rationalize the outcome of the ring opening, two plausible mechanisms were postulated. The first one is via a nonclassical carbocation rearrangement. Nonclassical cyclobutyl and cyclopropylmethyl carbocations have been extensively studied.[146-149] Upon formation of the carbocation, a pentacoordinated cation with strong transannular bonding is formed (Figure 3.3).[146]

In pioneering studies, it was calculated that a cyclobutyl carbocation was 0.5 kcal/mol more stable than the cyclopropylmethyl carbocation (for R = H).[147] The activation barrier between the two cyclic isomers was calculated to be 0.6 kcal/mol. Compared to the cyclic isomers, the homoallyl carbocation was calculated to be much less stable. Although its reduced steric hindrance would make it more susceptible to nucleophilic substitution, the homoallyl corresponding adduct was generally not observed, with exceptions depending on the nature and position of the substituents. The computational studies later agreed with experimental data.[148] The interconversions between the carbocation rearrangements were stereospecific.[149] Upon nucleophilic quench, the ratio of isomers is dictated by the Curtin-Hammett principle and depends on the substituents. The product distribution reflects the difference in energy between the rate-limiting transition states. Since the ratio of isomers and the rate-limiting transition states depend on both the nucleophile (Nu) and the nature and position of substituents on the BCB, it will be illustrated *vide infra* (Tables 3.4-3.5, Scheme 3.16) Another plausible mechanism is the concerted nucleophilic attack and protonation on BCB under acidic conditions.

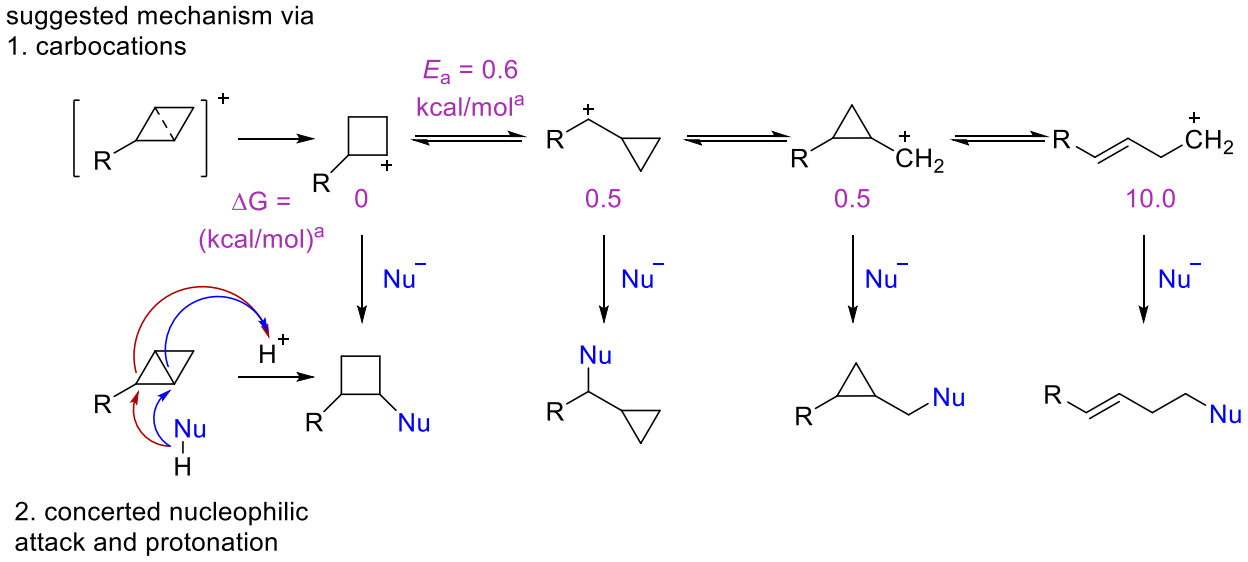
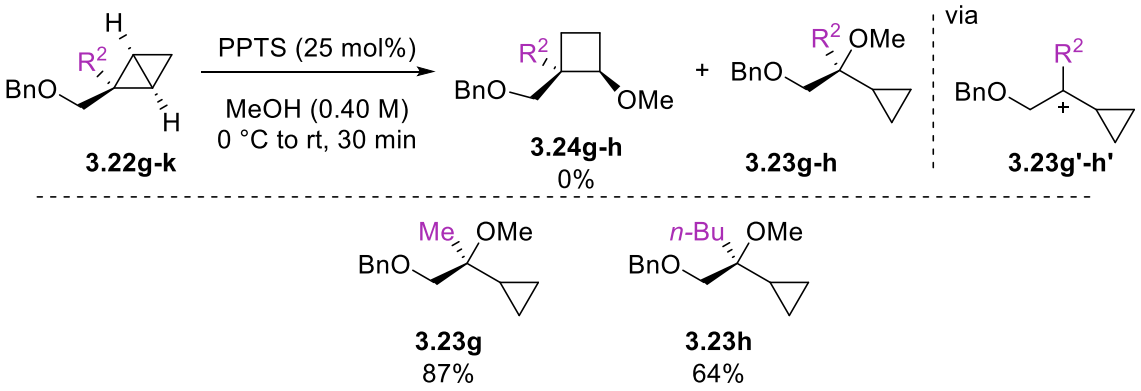


Figure 3.3 Nonclassical carbocations rearrangements. [a]For R = H.[147]

When the ring opening of other BCBs was studies, different isomeric products were obtained depending on the BCB substitution pattern (Tables 3.4 and 3.5). When the 2,2-disubstituted BCB **3.22g** was submitted to acidic conditions in methanol, only mono-substituted cyclopropane **3.23g** was isolated in an 87% yield (Table 3.4). Under acid-catalyzed ring-opening reaction, 2,2-

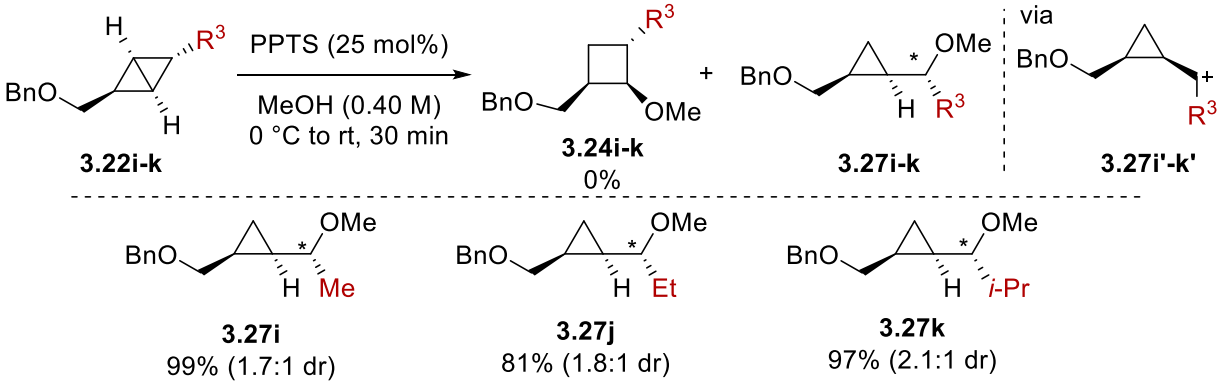
disubstituted BCB **3.22h** provided a single isomer of cyclopropane **3.23h** in 64% yield. In both cases, no cyclobutane **3.24g-h** was observed.

Table 3.4 Acid-catalyzed ring opening of 2,2-disubstituted BCBs.



For the 2,4-disubstituted BCBs **3.22i-k**, the 1,2-disubstituted cyclopropane **3.27-k** were obtained in excellent to quantitative yields, albeit in poor ratios of diastereomers (Table 3.5). Indeed, methanol can attack from either side of the carbocation **3.27i'-k'**. In all cases, no cyclobutane **3.24i-k** was observed.

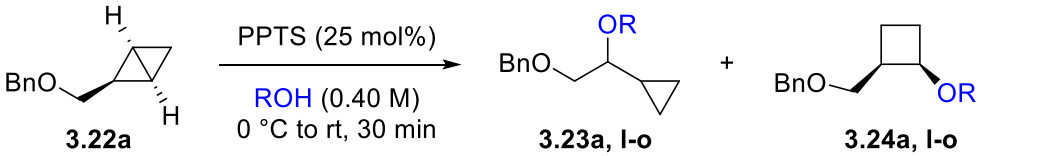
Table 3.5 Acid-catalyzed ring opening of 2,4-disubstituted BCBs.



BCB **3.22a** was submitted to the acid-catalyzed nucleophilic ring opening reaction using various alcohols (Table 3.6). With methanol, 54% of the cyclopropane **3.23a** along with 14% of cyclobutane **3.24a** were obtained (entry 1). With both ethanol and allyl alcohol as the nucleophile, a ratio of cyclopropane/cyclobutane of 3:1 was obtained (entries 2 and 3). Cyclopropanes **3.23l** and **3.23m** were respectively isolated in 36% and 30% yield. With isopropanol, 28% of cyclopropane **3.23n** along with 6% of cyclobutane **3.24n** were obtained (entry 4). The PPTS-catalyzed addition

of a solution of phenol in dichloromethane provided 22% of the corresponding cyclopropane **3.23o** (entry 5). Unfortunately, compared to methanol, the ratio of cyclobutane could not be improved with all the other alcohols that were tested.

Table 3.6 Alcohol and phenol addition to electron rich 2-substituted BCB **3.22a**.



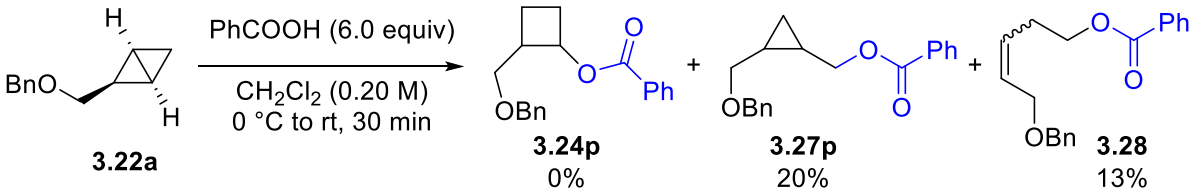
R = Me, **3.23a**, **3.24a**
= Et, **3.23l**, **3.24l**
= $CH_2CH{=}CH_2$, **3.23m**, **3.24m**
= *i*-Pr, **3.23n**, **3.24n**
= Ph, **3.23o**, **3.24o**

Entry	R	Yield		Ratio
		3.23 (%)[a]	3.24 (%)[b]	3.23:3.24[b]
1	CH_3	54	14	4:1
2	CH_2CH_3	36	13	3:1
3	$CH_2CH{=}CH_2$	30	11	3:1
4	$CH(CH_3)_2$	28	6	4:1
5	C_6H_5[c]	22	-	1:0

[a]Isolated yield. [b]Determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard in crude reaction mixture. [c]10 equivalents of a 0.40 M solution of PhOH in CH_2Cl_2.

During pioneered studies on unsubstituted cyclobutyl carbocation, the homoallyl carbocation was calculated to have a higher relative energy of 10 kcal/mol and 10.5 kcal/mol respectively compared to the cyclobutyl and methylcyclopropyl carbocations (Figure 3.3).[147] However, Wiberg observed the exclusive formation of adduct resulting from the homoallyl carbocation during acetolysis on 3-substituted cyclobutyl carbocation.[149] It was postulated that the formation of the homoallyl ion occurs after the rate-determining step of the acetolysis. In other words, although the rate-determining step involves a bicyclo[1.1.0]butyl carbocation transition state, the rearrangements to cyclopropylmethyl and homoallyl carbocations take place after this step.[146]

When benzoic acid was used a nucleophile to open BCB **3.22a**, it provided a mixture of isomers consisting of cyclopropane **3.27p** and homoallylic ester **3.28** in a combined 33% yield (Scheme 3.16). No cyclobutane **3.24p** was observed. The effect of the stoichiometry and the concentration were also studied, without any improvement.



Scheme 3.16 Benzoic acid addition to electron rich BCB **3.22a**.

From all the acidic conditions attempted on BCB **3.22a**, mixtures of isomers composed of cyclobutane-, methylcyclopropane- and acyclic butene-derived products were obtained. Alternatively, 2,2-disubstituted BCB **3.22g-h** and 2,4-disubstituted BCBs **3.22i-k** both reacted efficiently under acidic conditions to provide single cyclopropane isomers. Optimization did not increase the formation of the corresponding cyclobutane in any case. The transformation was limited considering that the major cyclopropane products could be synthesized by more efficient methods.

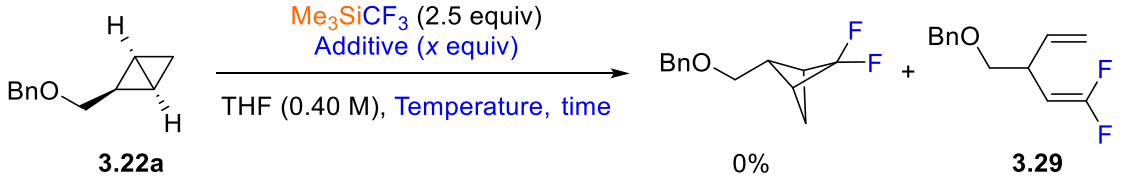
3.5.2 Electron Rich 2-Substituted BCBs in [2+1] Cycloadditions

BCB **3.22a** was submitted to cycloaddition conditions in which the HOMO of the central C–C bond would act as a two-electron donor. In the following section, [2+1] cycloadditions using a difluorocarbene and a metal carbene were attempted using established protocols.

The addition of a difluorocarbene to BCB esters to supply 2,2-difluoro-bicyclo[1.1.1]pentane (F_2-BCP) was reported in 2019 (Scheme 1.10).[50,51] BCB **3.22a** was submitted to conditions which generate difluorocarbene (Table 3.7). Initially, *in situ* generated difluorocarbene from trimethyl(trifluoromethyl)silane and sodium iodide was added to BCB **3.22a** (entry 1). Although no desired F_2-BCP was observed, another product **3.29** was obtained. When the activation of trimethyl(trifluoromethyl)silane was promoted with difluorotriphenyl silicate (TBAT), 38% of starting material **3.22a** was recovered along with 15% of difluoropentadiene **3.29**, but no desired F_2-BCP was observed (entry 2). Since it was postulated that difluoropentadiene **3.29** was a degradation product of F_2-BCP, milder conditions were attempted to favour the isolation of

F_2-BCP. Although difluorocyclopropanations of alkenes often required heating with sodium iodide (Figure 3.4a),[150] full conversion of BCB **3.22a** was observed at room temperature (Table 3.6, entry 3). Moreover, the reaction was completed at room temperature after one hour, with no formation of desired F_2-BCP (entry 4). Hence, the stability of BCB **3.22a** toward trimethyl(trifluoromethyl)silane was tested and only BCB **3.22a** was quantitatively recovered (entry 5).

Table 3.7 Difluorocarbene addition to an electron-rich 2-substituted BCB **3.22a**.



3.22a 0% **3.29**

Entry	Additive	Equivalent of additive (*x*)	Temperature	Time (h)	Yield	
					3.22a (%)[a]	**3.29 (%)[a]**
1	NaI	0.20	65 °C	2	-	30
2	TBAT	0.05	rt to 50 °C	8	38	15
3	NaI	0.20	rt	2	-	37[b]
4	NaI	0.20	rt	1	9	33
5	-	-	rt	2	99	-

[a]Yield determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

[b]Isolated yield.

Two mechanisms were reported to explain the formation of difluoropentadiene from the addition of difluorocarbene to BCB carboxylate **3.4**. Ma postulated that BCB **3.4** degrades to a carbene upon heating (Figure 3.4b).[50] Difluorocarbene would then react with the resulting carbene intermediate to provide difluoropentadiene. Alternatively, Mykhailiuk proposed a stepwise mechanism, in which a carbocation intermediate was invoked (Figure 3.4c).[51] The cyclobutyl carbocation obtained by the reaction of the C–C central bond (**3.4**) with difluorocarbene would then undergo a ring-opening process to form difluoropentadiene. Further limitations of the methodology were outlined.[151] For example, the removal of the electron withdrawing group on the aryl substituent and/or the addition of an electron donating group significantly decreased the yield. Since previous reactions on BCB **3.22a** suggested the formation of carbocations (Section 3.5.1)

and since substrate **3.22a** lacked a substituent to stabilize an anion (Figure 3.2, path b), it was hypothesized that the formation of **3.29** would most likely go through the formation of a carbocation (Figure 3.4d). As the 1-position of BCB is unsubstituted, a cyclobutyl secondary carbocation from BCB **3.22a** is less stabilized than the tertiary cyclobutyl carbocation from 1,3-disubsituted BCB **3.4**.

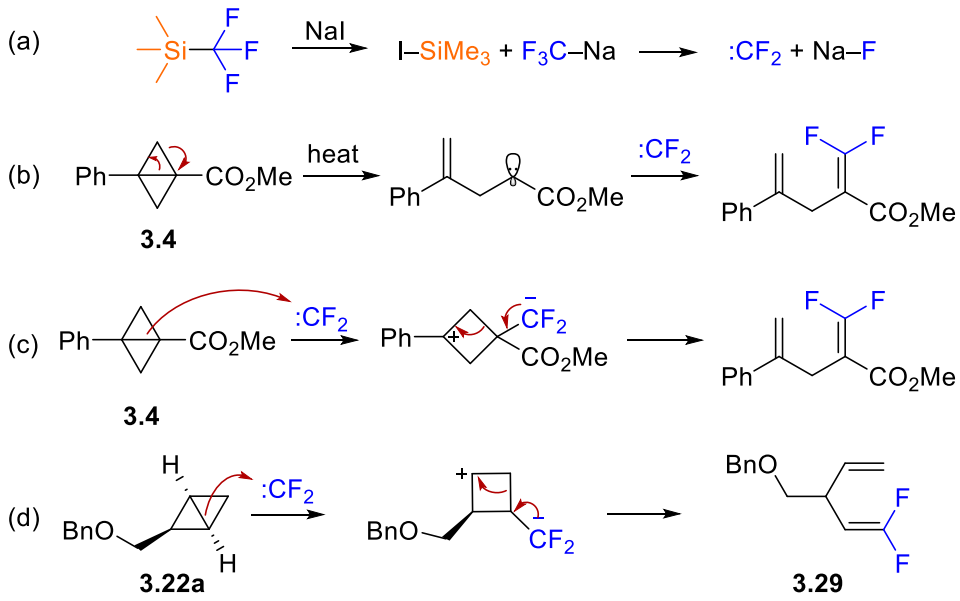
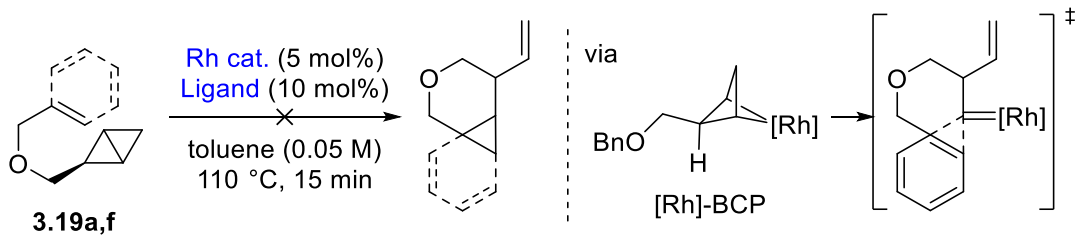


Figure 3.4 Postulated mechanisms for the formation of difluoropentadiene.

Conditions for rhodium-catalyzed cycloisomerization were tested using BCB **3.22a**. In reported conditions, a 5- or 7-membered ring was obtained depending on the steric hindrance of the catalyst (Scheme 1.11).[52] Since BCB **3.22a**, has only one substituent on position 2, the ring-opening reaction of the resulting rhodium-containing bicyclo[1.1.1]pentane (BCP) intermediate would provide the same product for both catalysts upon rhodium insertion. When submitted to rhodium catalysts, starting material **3.22a** was not recovered (Table 3.8, entries 1 and 2), so it was postulated that Rh did insert in BCB C(1)-C(3) bond. However, the resulting mixture contained many products, which were formed in low yields. To reduce the required energetically demanding dearomatization of the benzyl group, it was replaced with an allyl substituent in BCB **3.22f** (entries 3-6). Although results seemed promising as no BCB **3.22f** was recovered, BCB **3.22f** could also not tolerate high temperatures. No substantial amount of desired product was isolated for analysis, even after a scale-up (entry 6). It was postulated that the allyl substituent might not be electron rich enough to react with carbo-Rh-BCP complex.

Table 3.8 Rhodium-catalyzed cycloisomerisation of electron rich 2-substituted BCBs **3.22**.



Entry	Substrate	Scale (mmol)	Rh Cat.	Ligand
1	**3.22a**	0.2	$[Rh(C{=}C)_2Cl]_2$	PPh_3
2	**3.22a**	0.2	$[Rh(C{=}O)_2Cl]_2$	dppe
3	**3.22f**	0.2	$[Rh(C{=}C)_2Cl]_2$	PPh_3
4	**3.22f**	0.2	$[Rh(C{=}O)_2Cl]_2$	dppe
5	**3.22f**	0.2	$Rh(PPh_3)_3Cl$[a]	-
6	**3.22f**	0.6	$[Rh(C{=}C)_2Cl]_2$	PPh_3

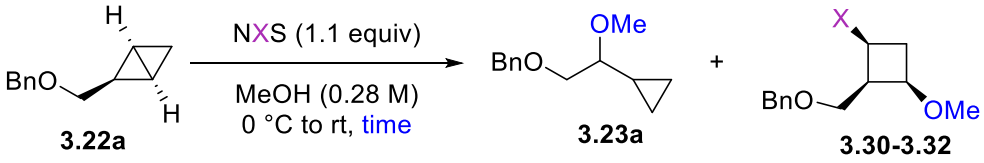
[a]Entry done with 10 mol% catalyst loading.

3.5.3 Electrophilic Additions to an Electron Rich 2-Substituted BCB

Since nucleophilic additions and cycloadditions were unsuccessful, the reaction with electrophilic halides was studied. To synthesize the corresponding halocyclobutane products, *N*-chloro, -bromo or -iodosuccinimide were added to BCB **3.22a** (Table 3.9). Upon addition of *N*-chlorosuccinimide (NCS), no desired chlorocyclobutane **3.30** was observed, but only cyclopropane **3.23a** was isolated in 40% yield (entry 1). When *N*-bromosuccinimide (NBS) was added, a mixture of cyclopropane **3.23a** and bromocyclobutane **3.31** were obtained (entry 2). Alternatively, upon addition of *N*-iodosuccinimide (NIS), an increased 56% yield of 2-iodo-4-methoxycyclobutane **3.32** was observed along with traces of cyclopropane **3.23a** (entry 3). The reaction with NIS was then further optimized. With longer reaction times, iodocyclobutane **3.32** was observed in a low 14% yield and cyclopropane **3.23a** was obtained as the major product in 33% yield (entry 4). The optimal reaction time was 30 minutes (entry 5). However, the results were difficult to reproduce even with freshly recrystallized NIS. To avoid the formation of HI as much as possible, the protocol was improved with a solution of NIS in THF (1.0 M). The optimal conditions provided

iodocyclobutane **3.32** in an isolated 77% yield (entry 6). Fortunately, the reaction of BCB **3.22a** with NIS provided diastereoselectively iodocyclobutane **3.32**.

Table 3.9 Halogen addition to an electron rich 2-substituted BCB **3.22a** using electrophilic sources of halogens.



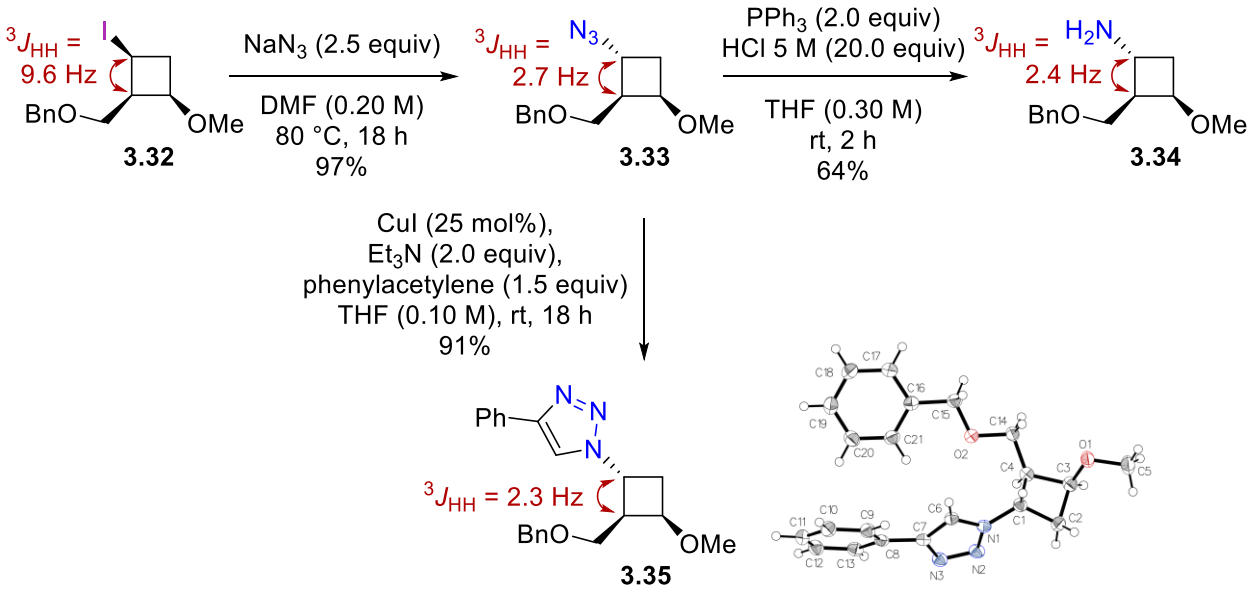
3.22a **3.23a** **3.30-3.32**

Entry	X	Desired corresponding product	Time (h)	Yield	
				3.23a (%)[a]	3.30-3.32 (%)[a]
1	Cl	**3.30**	3.0	40	-
2	Br	**3.31**	3.0	21	15
3	I	**3.32**	3.0	<5	56
4	I	**3.32**	18.0	33	14
5	I	**3.32**	0.5	-	67
6	I	**3.32**	0.5	-	77[b]

[a]Yield determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

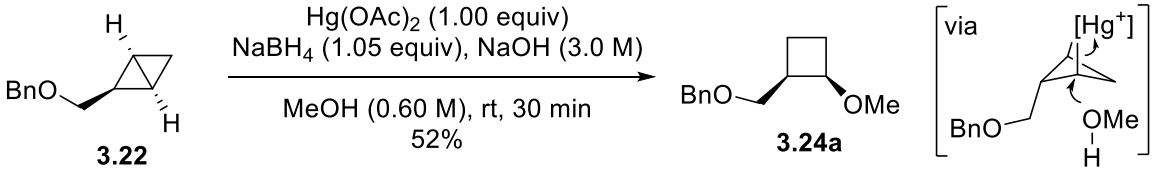
[b]Isolated yield using a NIS in solution (1.0 M in THF).

The coupling constant between C*H*I and $C_{cyclobutyl}$*H*CH_2OBn was measured to be 9.6 Hz in ^{1}H NMR, which confirmed the all-*cis* configuration of **3.32**. Iodocyclobutane **3.32** was further derivatized and afforded good to excellent yields of highly valuable cyclobutylazide **3.33** and derivatives **3.34** and **3.35** (Scheme 3.17). Upon Staudinger reduction of the azide,[152] cyclobutylamine **3.29** was smoothly obtained in a 64% yield. Alternatively, cyclobutyltriazole **3.35** was obtained from a [3+2] cycloaddition with phenylacetylene in an excellent 91% isolated yield. The structure of cyclobutyltriazole **3.35** was confirmed by X-ray crystallography to reveal that the triazole substituent was in *trans* configuration to other functional groups. Since the coupling constants between C*H*N and $C_{cyclobutyl}$*H*CH_2OBn of cyclobutyl amines **3.33-3.35** all had values of 2.3 to 2.7 Hz and that cyclobutyltriazole **3.35** configuration was confirmed by X-ray crystallography, it confirmed the all-*cis* configuration of iodocyclobutane **3.32**.



Scheme 3.17 Derivatization of iodocyclobutane **3.32** to aminocyclobutanes.

Lastly, BCB **3.22a** was submitted to oxymercuration-demercuration conditions to provide cyclobutane **3.24a** as a single diastereomer in a 52% yield (Scheme 3.18). Similar to previously postulated rhodium-bicyclo[1.1.1]pentane (BCP) intermediate,[52] it was hypothesized that the central bond of BCB **3.22a** would attack as a nucleophile, providing a mercurium-BCP intermediate (Scheme 1.11). The subsequent attack of methanol would lead to the single diastereomer cyclobutane **3.24a**.



Scheme 3.18 Oxymercuration-demercuration of electron rich 2-substituted BCB **3.22**.

3.6 Conclusion

To summarize, a clean 3-step synthesis of electron rich BCBs was accomplished using readily available reagents and generate 2, 2,2- and 2,4-substituted electron-rich BCBs without purification. To the best of our knowledge, the synthesis of 2,2-disubstituted BCBs has never been reported before. As opposed to previous work on electron poor BCBs, electron rich 2-subsituted BCBs were reactive towards electrophiles and acidic conditions. From all the attempted

functionalization reactions, electron rich 2-substituted BCB demonstrated stability to cycloadditions, basic and nucleophilic additions.

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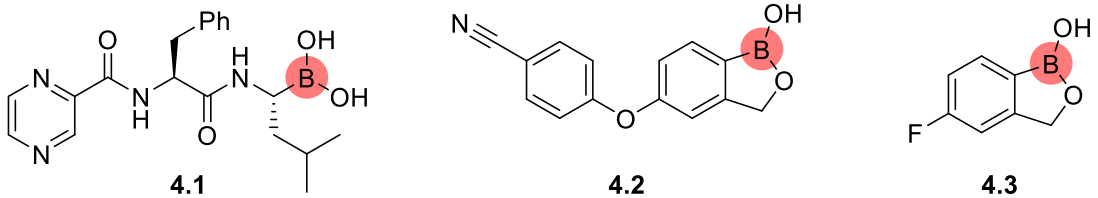
4. Development of a Visible-Light Mediated *gem*-Borosilylcyclopropanation

4.1 Introduction to *gem*-Borosilylcyclopropanes

4.1.1 Boron and Silicon in Bioactive Molecules

Boronate and silyl units are frequently found in active pharmaceutical agents or drug candidates, in addition to being useful synthons and powerful functionalization groups.[153] For instance, boron-containing active pharmaceutical ingredients, such as bortezomib **4.1**, crisaborole **4.2** and tavaborole **4.3**, were approved by the US Food and Drug Administration (FDA) and European authorities in the past few decades (Figure 4.1).[154] The α-amino boronic acid bortezomib **4.1** was used as a bioisostere of a typical amino acid linked to a dipeptide backbone. Involved with the treatment of blood cancer, it was the first approved proteasome inhibitor. Its specific mode of action, proposed as complexation of the threonine hydroxy group in the active site of a proteasome involved in regulation of cell proliferation, was attributed to the boronic acid moiety.[155] During structure-activity relationship screening for an atopic dermatitis target, which is involved in an allergic skin disorder, crisaborole **4.2** was found to have an increased potency among a series of phenoxybenzoxaborole anti-inflammatory agents.[156] Another example is tavaborole **4.3**, which tackles the difficult drug penetration of fingernails in fungal infection treatment, and maximizes nail penetration after topical application during the treatment of onychomicosis.[157]



4.1
bortezomib
anticancerous

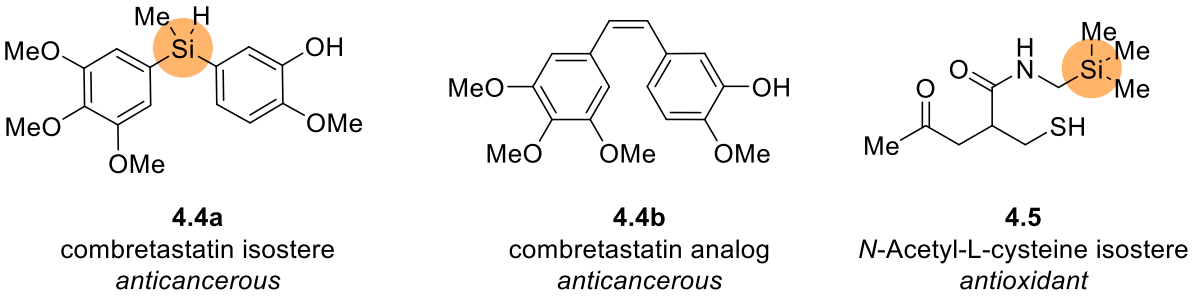
4.2
crisaborole
atopic dermatitis treatment

4.3
tavaborole
antifungal

Figure 4.1 Examples of boron-containing active pharmaceutical ingredients.

On the other hand, pharmacodynamic properties of drug candidates were improved when C=C bonds were replaced with a C–Si bond.[158] Silicon is the 2nd most abundant atom on earth after

oxygen and is non-toxic under various forms.[159] The tetrahedral silicon atom can be an alternative to carbon in medicinal chemistry. Combretastatin, possessing a *cis*-olefin, was initially used to target tubulin polymerization- and tumor growth-inhibitory activities in cell proliferation (Figure 4.2).[160] However, since it isomerizes spontaneously to the inactive *trans*-alkene form, the double bond was replaced with a silicon atom (derivative **4.4**) during structure-activity relationship studies. Since the calculated distance between the two aromatics is 3.00 Å with an alkene and 3.03 Å with a silicon atom, silane **4.4a** was developed and found to exhibit similar activity compared to its parent analog **4.4b**. Additionally, silane **4.5** was reported to be a better radical scavenger than its parent analogue *N*-acetyl-L-cysteine, which is already a powerful antioxidant. Since adding a (trimethylsilyl)methyl to the primary amine significantly improved its lipophilicity, silane **4.5** was able to cross the blood-brain barrier, making it relevant for therapeutic applications for Alzheimer's and Parkinson's diseases and multiple sclerosis.[161] The examples demonstrate that silyl group incorporation provides a general strategy to modulate the toxicity, the lipophilicity and the size of drug candidates. The incorporation of boronate and silyl functionalities ultimately offers unique properties for drug design.



4.4a
combretastatin isostere
anticancerous

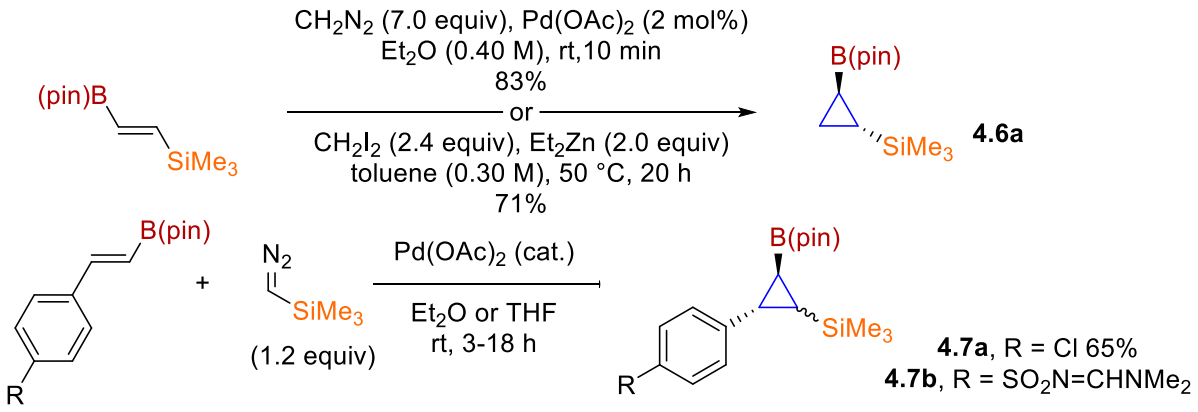
4.4b
combretastatin analog
anticancerous

4.5
N-Acetyl-L-cysteine isostere
antioxidant

Figure 4.2 Examples of silicon-containing drug candidates.

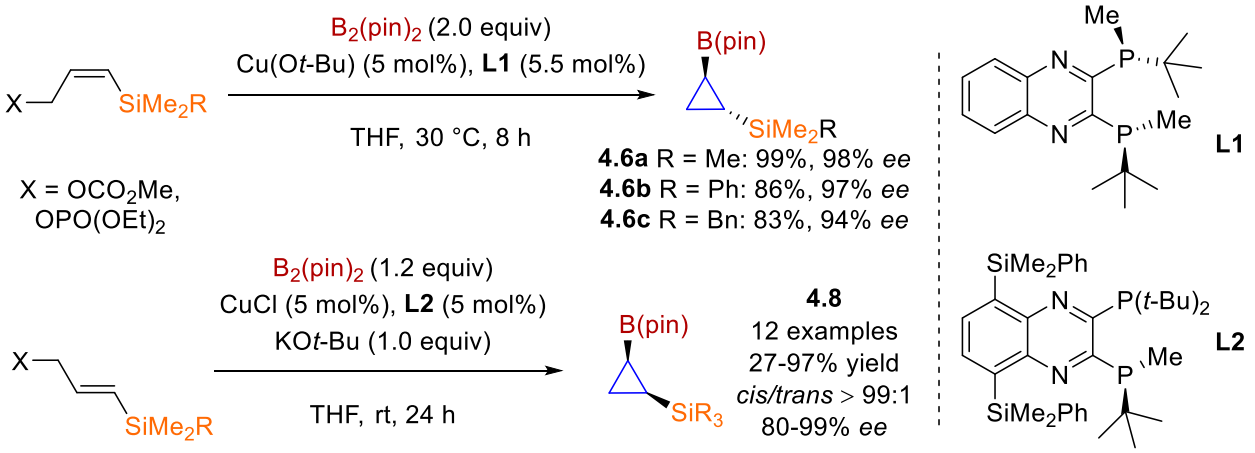
4.1.2 Previous 1,2-Borosilylcyclopropane Syntheses

A few syntheses of borocyclopropylsilanes have been reported in the literature. In 1989, Carboni was the first to describe the synthesis of a 1-boro-2-silylcyclopropane **4.6a** using a ((silyl)vinyl)boronate ester and diazomethane (Scheme 4.1).[162] Simmons-Smith type conditions leading to the same product with 71% yield were later published by the same group.[163] Similarly, the decomposition of trimethylsilyldiazomethane was employed along with ((aryl)vinyl)boronates to synthesize 1-aryl-2-boro-3-silylcyclopropanes **4.7**.[164]



Scheme 4.1 Syntheses of 1-boro-2-silylcyclopropanes via decomposition of diazo compounds.

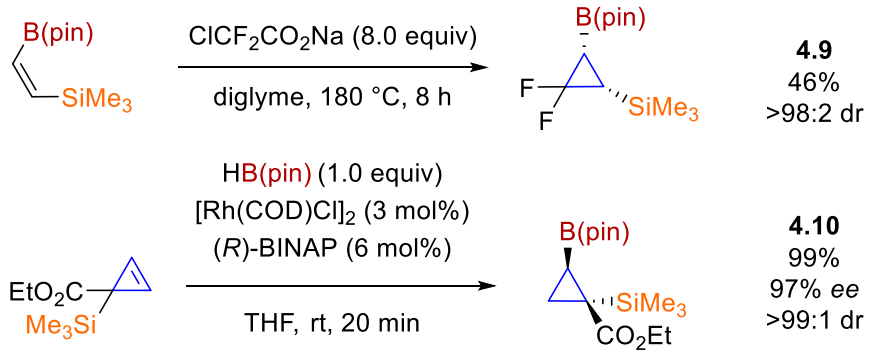
In 2008, Ito and Sawamura reported a copper-catalyzed enantioselective synthesis of *trans*-borosilylcyclopropanes **4.6a-c** from *Z*-silylated allylic carbonates while using a chiral ligand and bis(pinacolato)diboron (Scheme 4.2).[165] Three examples comprising different silyl groups lead to the desired motif. To achieve the complimentary *cis*-borosilylcyclopropanes **4.8**, conditions in which a bulkier ligand was used, were recently optimized with *E*-silylated allylic carbonates.[166] The corresponding *cis*- and *trans*-cyclopropanes were both obtained in excellent yields and excellent enantioselectivities.



Scheme 4.2 Copper-catalyzed enantioselective synthesis of borosilylcyclopropanes.

Two examples of tri– or tetra–substituted borosilylcyclopropanes were reported as well. The synthesis of difluorosilylcyclopropyl boronate **4.9** from a ((silyl)vinyl)boronate ester was described by Amii using an excess of sodium chlorodifluoroacetate as a difluorocarbene precursor (Scheme 4.3).[167] The conditions required high temperatures and furnished a single example of a

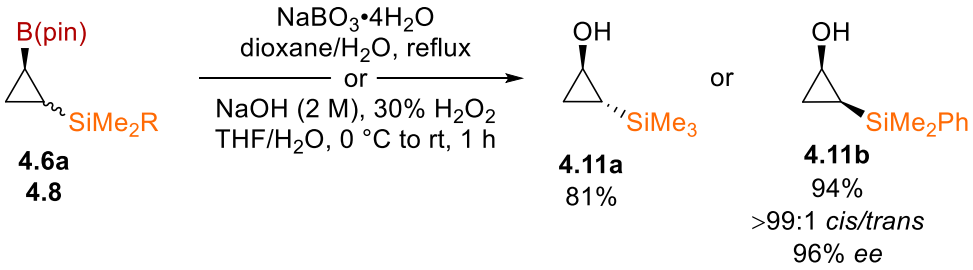
borosilylcyclopropane in moderate yields. In 2003, Gevorgyan described a hydroboration reaction on a silylcyclopropene.[168] Although yields, enantio– and diastereo–selectivities were excellent, a single borosilylcyclopropane **4.10** was obtained using the conditions. In addition to the low structural diversity reported by the methods, previous instances of borocyclopropyl silanes are limited. Therefore, the development of a direct methodology and scalable synthesis of the compounds would represent a significant contribution to the field.



Scheme 4.3 Syntheses of substituted 1-boro-2-silylcyclopropanes.

4.1.3 Previous Work on the Functionalization of Borosilylcyclopropanes

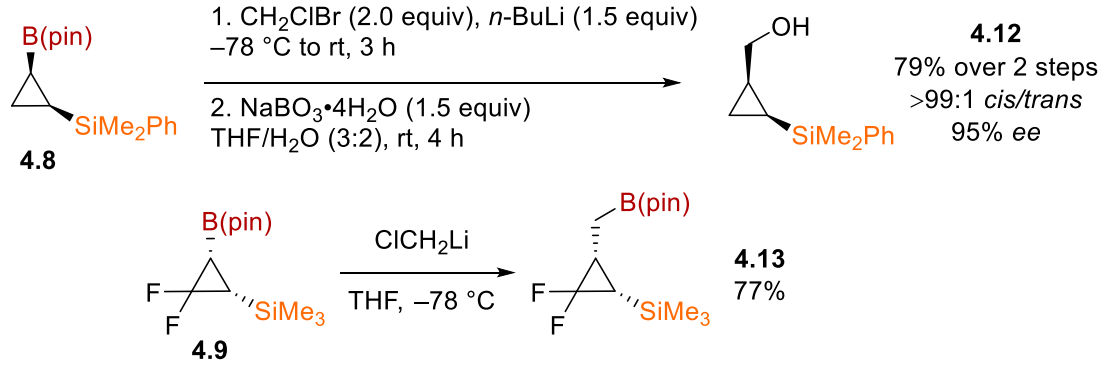
The previously synthesized borosilylcyclopropanes **4.6a, 4.8** and **4.9** were engaged in post-functionalization reactions. The selective oxidation of the boronate ester provided cyclopropanols **4.11** in high yields with retention of stereochemistry (Scheme 4.4).[165,166]



Scheme 4.4 Oxidation of borosilylcyclopropanes to silylcyclopropanols.

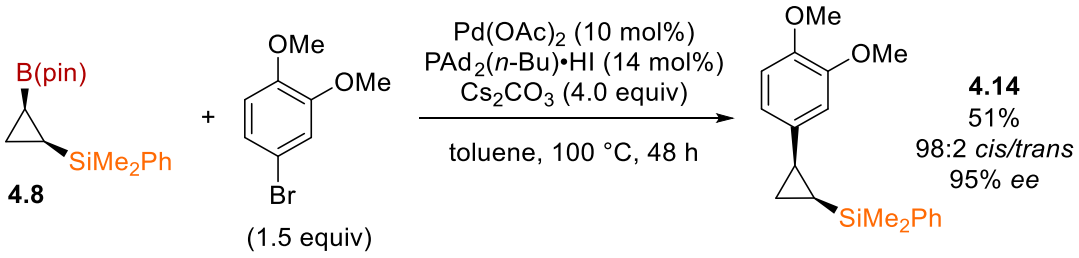
Two applications of the Matteson homologation on borosilylcyclopropanes **4.8** and **4.9** were described (Scheme 4.5). In the first example, the resulting cyclopropylmethylboronate was immediately submitted to oxidation conditions to obtain cyclopropylmethanol **4.12** with retention

of stereochemistry in 79% yield over 2 steps.[166] Tetra-substituted difluorocyclopropane **4.9** was submitted to the Matteson homologation to obtain the desired boronate **4.13** in 77% yield.[167]



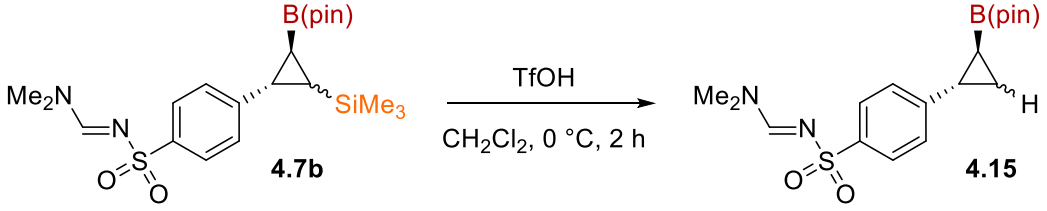
Scheme 4.5 Matteson homologation of borosilylcyclopropanes to (2-silylcyclopropyl)methanes.

Borosilylcyclopropane **4.8** was engaged in a Suzuki-Miyaura cross-coupling with excellent retention of diastereo– and enantioselectivities to provide arylcyclopropyl silane **4.14** (Scheme 4.6).[166] Although cross-coupling yields with the electron-rich electrophilic partner *m,p*-dimethoxyphenyl bromide are usually good, only 51% of the desired coupling adduct was obtained. The low yield might be explained by the increased steric hindrance caused by the *cis*-silyl functional group.



Scheme 4.6 Suzuki-Miyaura cross-coupling of a borosilylcyclopropane.

The post-functionalization reactions involving the silyl substituent of borosilylcyclopropane are currently limited to the proto-desilylation (Scheme 4.7).[164b]



Scheme 4.7 Protodesilylation of a borosilylcyclopropane.

To summarize, the exploration of the reactivity of borosilylcyclopropanes remained limited since their syntheses are scarce. Among the previously reported functionalization reactions of borosilylcyclopropanes, none of the previously reported publications explored their orthogonal reactivity.

4.2 Research Goals

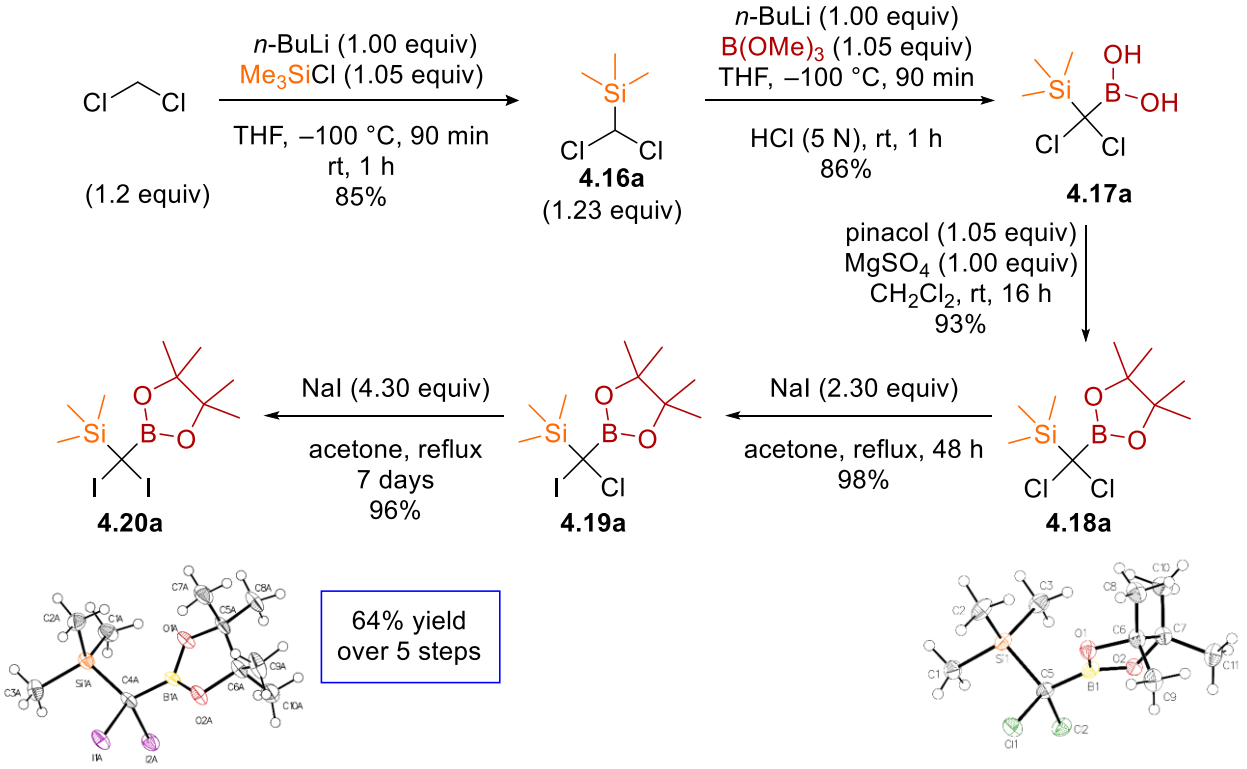
To the best of our knowledge, the preparation of *gem*-borosilylcyclopropanes has never been reported in the literature. Inspired by the previous photochemical cyclopropanation reactions reported by our group,[120] the goals of the project were to (1) develop a convenient, user-friendly and operationally simple method to prepare *gem*-borosilylcyclopropanes with high diastereoselectivity using mild reaction conditions; (2) study the scope of the reaction; and (3) develop orthogonal post-functionalization reactions. Furthermore, by taking advantage of the bulkiness of the trimethylsilyl substituent, the aim was to access *cis*-disubstituted-borocyclopropanes.

4.3 Diiodo(trimethylsilane)methylboronate Ester Synthesis

4.3.1 Background Information

A 5-step synthesis of diiodomethyl(trimethylsilyl)boronate ester **4.20a** was developed by Dr. Morgane Sayes, a former Ph.D. Charette group member (Scheme 4.8).[169] The first step involved the formation of a dichloromethyl anion from dichloromethane and *n*-butyllithium, which is then quenched with trimethylsilylchloride to obtain the commercially available and expensive dichloromethyltrimethylsilane **4.16a** in 85% yield. Sequential addition of *n*-butyllithium and trimethyl borate afforded the boronic acid **4.17a**, that was further converted into its pinacol ester **4.18a** in excellent yields. Dichloride reagent **4.18a** was quite reluctant to undergo a clean Finkelstein reaction when submitted to 2.3 equivalents of sodium iodide for 2 days. The first substitution occurred quite readily to afford chloroiodo reagent **4.19a** in 98% yield. The resulting adduct was then resubmitted to 4.3 equivalents of sodium iodide in acetone to supply the desired product **4.20a** after 7 days. Both chloroiodomethyl(trimethylsilyl)boronate ester **4.19a** and diiodomethyl(trimethylsilyl)boronate ester **4.20a** had their structures unambiguously confirmed by

X-ray crystallography. The first-generation synthesis sequence afforded 6.8 g of diiodomethyl(trimethylsilyl)boronate ester **4.20a** in an 57% yield over 5 steps.[169]



Scheme 4.8 Synthesis of diiodo(trimethylsilane)methylboronate ester **4.20a** from dichloromethane.

The $E^{Red}_{1/2}$(**4.20a**)= –1.28 V vs saturated calomel electrode (SCE) redox potential of borosilyldiiodomethane **4.20a** was determined by Sayes.[169] The maximum absorption of reagent **4.20a** was measured at 326 nm, in the UVA (Figure 4.3).

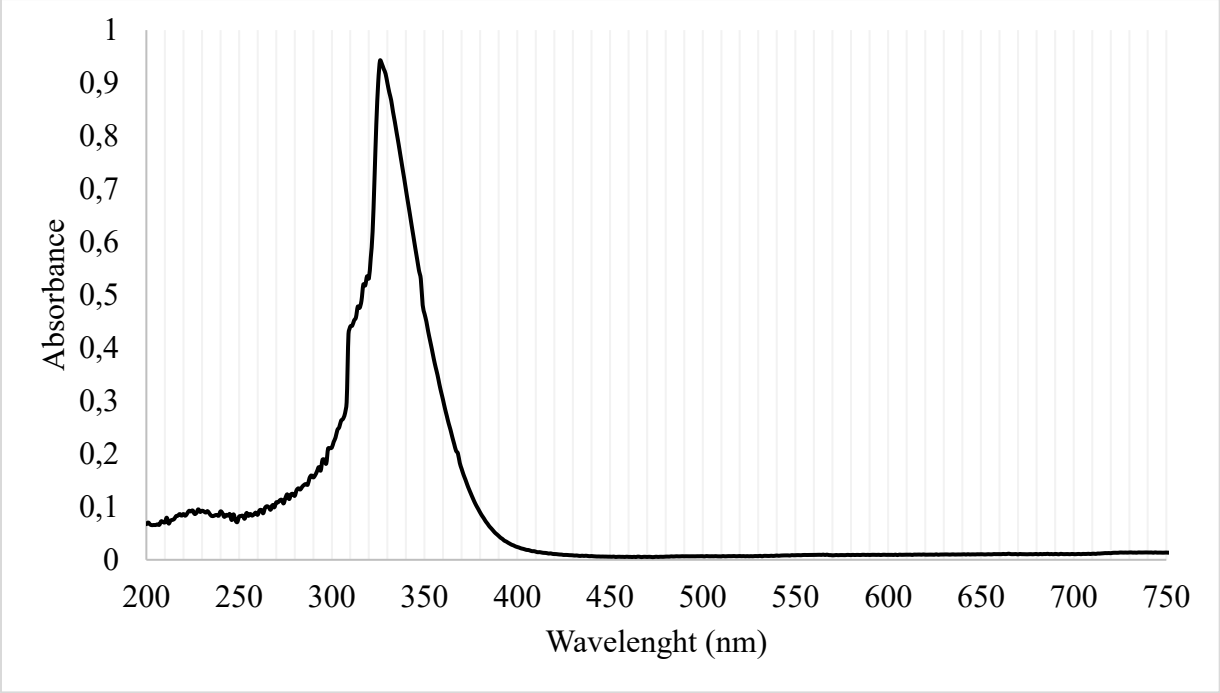
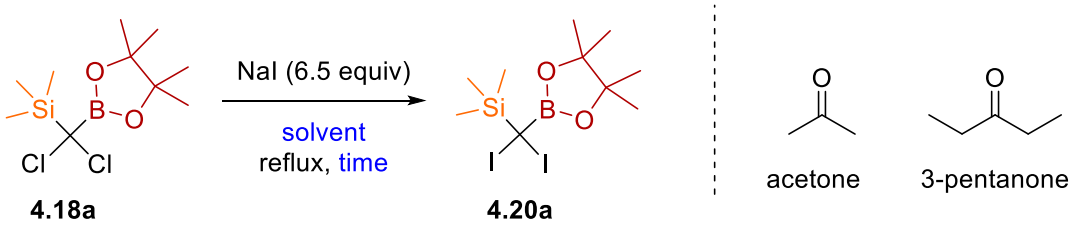


Figure 4.3 UV-vis absorbance of diiodomethyl(trimethylsilyl)boronate ester.

4.3.2 Optimization of the Synthesis of Diiodo(trimethylsilane)methylboronate Ester

The main drawback of the previous synthesis was the 9-day reaction of the last step (Scheme 4.8). The Finkelstein reaction afforded **4.20a** in 55% yield for the two steps on a 35-mmol scale using 6.5 equivalents of sodium iodide at 65 °C for 9 days (Table 4.1, entry 1). The reaction was repeated on a 55-mmol scale for 10 days, without isolation of the intermediate **4.19a**, to obtain 96% yield of **4.20a** (entry 2). The reaction was monitored by ^{1}H NMR and stopped upon full conversion of the starting material **4.18a**. ^{1}H NMR spectroscopy was the preferred method of analysis since both compounds **4.18a** and **4.20a** have the same retention factor on silica gel and starting material **4.18a** was not detected by mass spectrometry (LCMS or GCMS using electronic impact detection). To increase the rate of the double nucleophilic substitution reaction, the temperature was increased using 2-propanone instead of acetone as solvent. Unfortunately, only 36% of **4.20a** was isolated after 7 days (entry 3). Since the first step of the workup was a solvent switch, acetone was chosen as the preferred solvent due to its lower boiling point.

Table 4.1 Solvent optimization of the Finkelstein reaction of dichloride **4.18a**.



4.18a **4.20a**

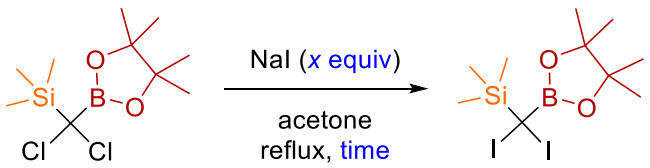
Entry	Scale (mmol)	Solvent	Temperature (°C)[a]	Time (days)	Yield 4.20a (%)[b]
1[c]	35	acetone	65	9	55
2	55	acetone	65	10	96
3	7	3-pentanone	105	7	36

[a]Temperature of the oil bath. [b]Isolated yield. [c]Experiment was run by Sayes in two steps.

Another strategy to carry out the transformation was to run the reaction under microwave irradiation instead of using an oil bath. Oil bath or heating mantle heating provides energy from the outside of the flask. For larger reaction vessels, the internal temperature might not be the same on the outside. A complimentary heating method uses microwaves to induce heating uniformly inside of the reaction vessel, thus allowing the reaction to reach higher temperatures than the boiling point of the solvent (in a sealed vessel). When the Finkelstein reaction was submitted to microwave irradiation, incomplete conversions and degradation were observed. The heat sensitivity of the product, coupled with the inability to scale up using our laboratory equipment, led us to abandon the approach.

Having studied the effect of the nature of the reaction solvent and heating method, the stoichiometry as a function of time was next investigated using acetone as the solvent (Table 4.2). The reaction was initially conducted over 10 days with 5.5 equivalents of sodium iodide (entry 1). The reaction was carefully monitored and stopped after full consumption of starting material **4.18a** with the remaining mass balance consisting of the intermediate **4.19a**. To shorten the reaction time, 8.0 and 9.5 equivalents of sodium iodide were tested (entries 2 and 3). Unfortunately, increasing the stoichiometry did not reduce the reaction time of 8 days and results were similar when using both 8.0 and 9.5 equivalents. The conditions using 8.0 equivalents of sodium iodide that gave a 96% isolated yield of **4.20a** (entry 2) were selected for the scale up process.

Table 4.2 Optimization of the equivalents of sodium iodide vs time of the Finkelstein reaction of dichloride **4.18a**.



4.18a **4.20a**

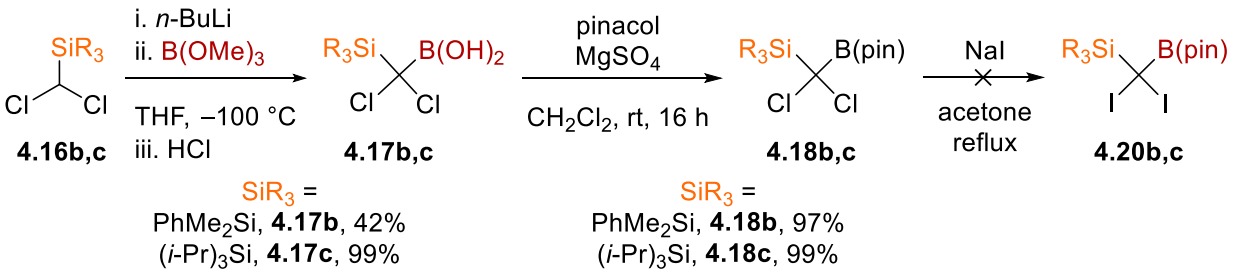
Entry	Equiv of NaI (*x*)	time (days)	Yield 4.20a (%)[a]
1	5.5	10	55
2	8.0	8	96
3	9.5	8	95

[a]Isolated yield.

The synthesis of the key reagent **4.20a** from dichloromethane was shortened by one step. The chromatography-free 4-step synthesis of diiodomethyl(trimethylsilyl)boronate ester **4.20a** was ultimately completed in 65% on 20-gram scale. Reagent **4.20a** was kept at –20 °C and did not show any sign of degradation over 3 years.

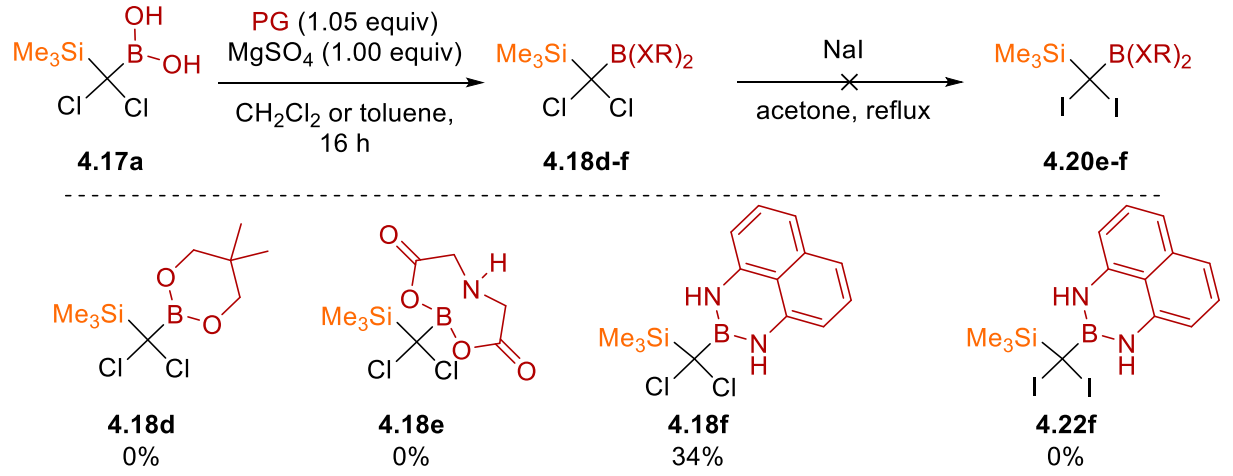
4.3.3 Attempts Toward the Synthesis of Other Borodiiodomethyl Silane Derivatives

The first three steps toward modification of the silyl substituent were successful and similar yields were obtained when compared to parent analog **4.20a** (Scheme 4.9). Dichloride **4.16c** was prepared from a known procedure.[170] Dimethylphenylsilyl derivatives **4.17b** and **4.18b** were prepared by Dr. Sayes, a former Ph.D. Charette group member.[169] When trimethysilyl was replaced by dimethylphenylsilyl or triisopropylsilyl, the Finkelstein reaction became problematic (**4.20b** and **4.20c**). Although some conversion was observed shortly at the beginning of the Finkelstein reaction for dimethylphenylsilane **4.18b**, the reaction stopped after 48 h. It was hypothesized that the first chloro/iodo exchange occurred as desired, but the formation of the second C–I bond did not proceed due to the increased steric hindrance. Similarly, when the trimethylsilyl group was replaced with triisopropylsilyl, no reaction was observed after 7 days of reaction.



Scheme 4.9 Attempts to prepare various borodiiodosilanes.

The syntheses of boron derivatives bearing various boronic acid protecting groups were attempted (Scheme 4.10). For both *neo*-pentyl variant **4.18d** and methyliminodiacetic acid (MIDA) **4.18e** variant, the protection of the boronic acid **4.17a** was challenging and no reaction took place. Conversely, the protection of the boronic acid **4.17a** with 1,8-diaminonaphtalene (dan) produced **4.18f** in 34% yield. However, the subsequent double Finkelstein reaction of **4.18f** led to deprotection and only the starting boronic acid **4.17a** was recovered.



Scheme 4.10 Attempts to generate other boron derivatives of borosilyldiodomethanes.

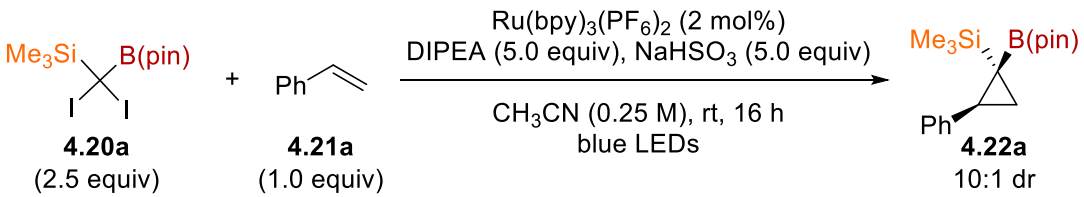
4.4 Optimization of the *gem*-Borosilylcyclopropanation Reaction

4.4.1 Preliminary Results

Preliminary results performed by Dr. Morgane Sayes were first inspired by conditions developed by Prof. Suero and involved replacement of diiodomethane[114] by diiodomethyl(trimethylsilyl)boronate ester **4.20a**. We were pleased to observe that a 78% ^{1}H NMR yield of borosilylcyclopropane **4.22a** was obtained (Table 4.3, entry 1).[169] Control experiments

were initially conducted to ensure that all the reaction components were necessary for the cyclopropanation. Removing the light source (entry 2) or the electron donor (entry 4) completely shut down the reaction. Conversely, a significant drop in the yield was observed if the reaction was run without the photocatalyst or without $NaHSO_3$ (entries 3 and 5).

Table 4.3 Control experiments of the light-mediated borosilylcyclopropanation reaction.

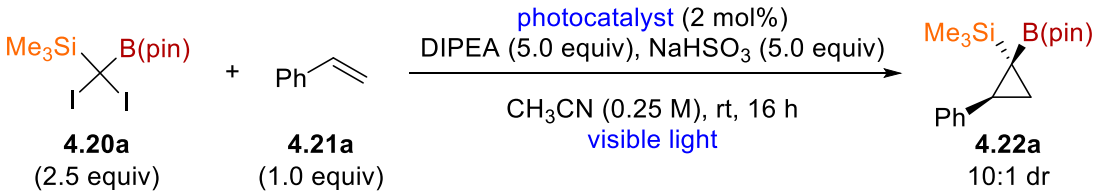


Entry	Deviation from standard conditions	Yield 4.22a (%)[a]
1	None	78
2	No light	0
3	No photocatalyst	43
4	No DIPEA	0
5	No $NaHSO_3$	41

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

The search for an optimal photocatalyst was also explored by Sayes (Table 4.4).[169] The photocatalysts that were tested were chosen based on a maximum absorbance in the visible light requirement and on the redox potentials. Either its E^{Ox}_{S1} or $E^{Red}½$ must lower than $E^{Red}½$(**4.20a**) = –1.28 V vs saturated calomel electrode (SCE).[169] Considering the high cost, and low sustainability of transition metal-based photoredox catalysts, we focused on efforts on testing organic photocatalysts (Figure 1.17).[171] The light source was chosen in accordance with the maximum absorption of the photocatalyst. Rose Bengal gave a reduced yield (entry 2). Fortunately and as predicted by redox potentials,[101] Eosin Y gave a yield similar to $Ru(bpy)_3PF_6$ (entry 3). 2,4,5,6-Tetrakis(9H-carbazol-9-yl)isophthalonitrile (4CzIPN), having a $E^{Red}½$ = –1.24 V, provided a lower 60% yield of cyclopropane **4.22a** (entry 4).

Table 4.4 Optimization of the photocatalyst of the light-mediated borosilylcyclopropanation reaction.



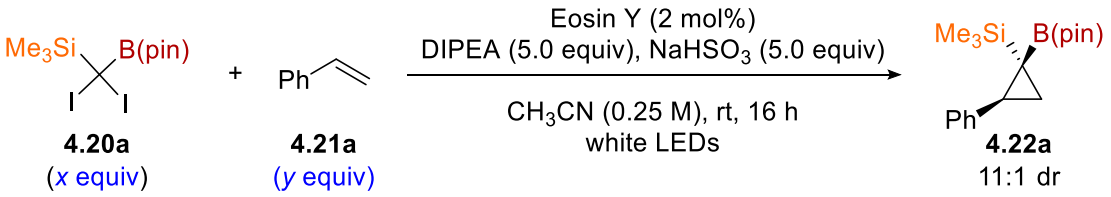
Entry	Photocatalyst	λmax (nm)[a]	Light Source	Yield 4.22a (%)[b]
1	$Ru(bpy)_3(PF_6)_2$	453	blue LEDs	78
2	Rose Bengal	549	white LEDs	63
3	Eosin Y	520	white LEDs	78
4	4CzIPN	435[c]	blue LEDs	60

[a]From reference 101. [b]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [c]Maximum absorbance from reference 172.

4.4.2 Screening Other Reaction Parameters

Following the preliminary optimization study by Sayes (Section 4.4.1),[169] other parameters were optimized using a new white LED strip to ensure reproducibility. First of all, the effect of the stoichiometry was studied (Table 4.5). Due to the high temperature produced by the old LED strip, the ratio of diastereomers was slightly better with the new LED strip. A ratio of 1:2 of styrene **4.21a** to reagent **4.20a** was initially used (entry 1). When the stoichiometric ratio of reactant **4.20a** to styrene **4.21a** was increased to 2.5:1.0 and 3.0:1.0, similar yields were observed (entries 2 and 3). Since **4.20a** must be synthesized in a 4-step sequence and is more expensive than the alkene, it was tested as the limiting reagent. Unfortunately, a 1.0:1.0 ratio led to a poor 44% yield (entry 4), but a 1.0:4.0 ratio afforded a 63% yield of the desired cyclopropane **4.22a** (entry 5).

Table 4.5 Effect of the stoichiometry of the light-mediated borosilylcyclopropanation reaction.



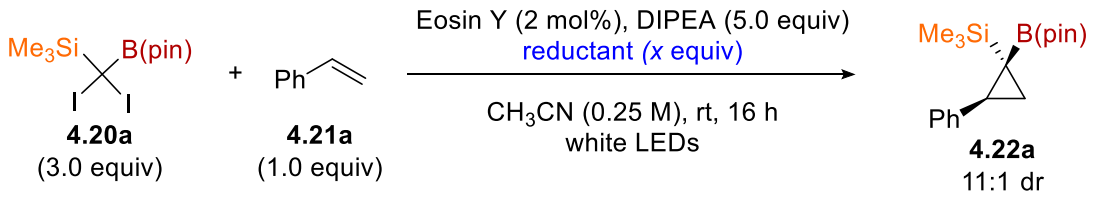
4.20a (*x* equiv) + **4.21a** (*y* equiv) → **4.22a** 11:1 dr

Entry	Equiv of 4.20a (*x*)	Equiv of 4.21a (*y*)	Yield 4.22a (%)[a]
1	2.0	1.0	78
2	2.5	1.0	77
3	3.0	1.0	79
4	1.0	1.0	44
5	1.0	4.0	63

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard based on the limiting reagent.

The effect of the reductant was studied as well (Table 4.6). $NaHSO_3$, $Na_2S_2O_3$ or the complete removal of the reductant gave similar yields (entries 1-3). However, the addition of the decahydrate of $Na_2S_2O_3$ (entry 4) was detrimental to the reaction. The number of equivalents of the reductant were next optimized (entries 5 and 6) leading to an optimal 2.5 equivalents to maximize the yield (84%) and diastereomeric ratio (11:1) of the desired products (entry 6).

Table 4.6 Effect of the reductant on the light-mediated borosilylcyclopropanation reaction.

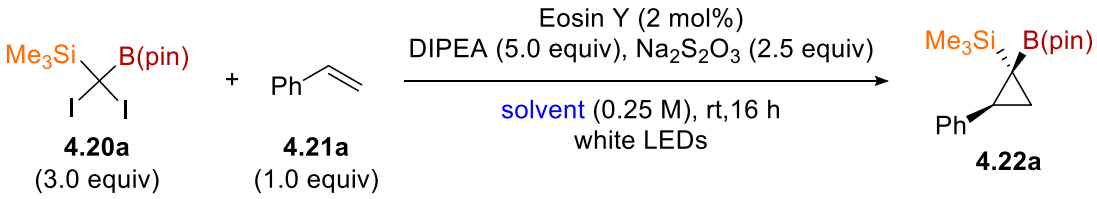


Entry	Reductant	Equiv of reductant (*x*)	Yield 4.22a (%)[a]
1	$NaHSO_3$	5.0	78
2	$Na_2S_2O_3$	5.0	79
3	-	-	73
4	$Na_2S_2O_5 \bullet 10H_20$	5.0	<5
5	$Na_2S_2O_3$	10.0	76
6	$Na_2S_2O_3$	2.5	80

[a]Yield of the combined diastereomers determined by ^1H NMR spectroscopy using triphenylmethane as the internal standard.

Numerous solvents were screened in the borosilylcyclopropanation reaction (Table 4.7). Among the solvents examines, the highest yields were obtained with acetonitrile and acetone (entries 1 and 9). Since acetone is inexpensive and it was classified as a recommended solvent based on eco-toxicity, health and safety,[173] it was the chosen as solvent for the rest of the optimization. In all cases, all organic solvents provided low to good conversions as long as they were anhydrous. Introduction of water to the solvent was detrimental to the reaction (entries 10 and 15).

Table 4.7 Effect of the solvent on the light-mediated borosilylcyclopropanation reaction.

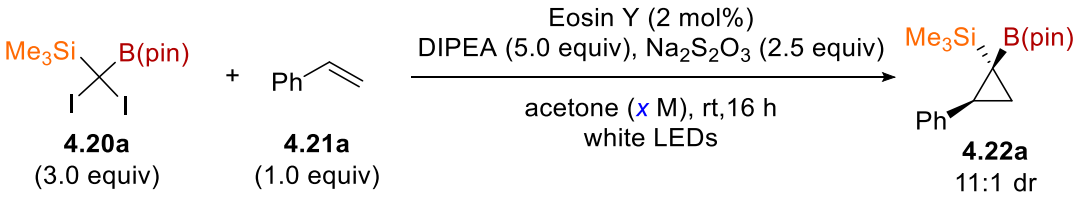


Entry	Solvent	Yield 4.22a (%)[a]	dr[b]
1	CH_3CN	80	11:1
2	CH_2Cl_2	53	14:1
3	THF	59	14:1
4	toluene	23	14:1
5	MeOH	27	13:1
6	1,2-DCE	40	14:1
7	1,4-dioxane	73	13:1
8	DMF	54	11:1
9	acetone	80	11:1
10	acetone/H_2O (20:1)	<5	-
11	EtOAc	46	13:1
12	DMSO	66	12:1
13	Et_2O	51	14:1
14	EtOH	52	16:1
15	EtOH/H_2O (95:5)	<5	-

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [b]determined by ^{1}H NMR spectroscopy analysis.

The effect of reaction concentration on the borosilylcyclopropanation reaction was next studied (Table 4.8). Lowering or increasing the reaction concentration did not seem to be beneficial to the reaction (entries 1 and 3). Nevertheless, yields and diastereoselectivity did not seem to be affected by changes in concentration between 0.15 and 0.5 M.

Table 4.8 Effect of the concentration on the light-mediated borosilylcyclopropanation reaction.



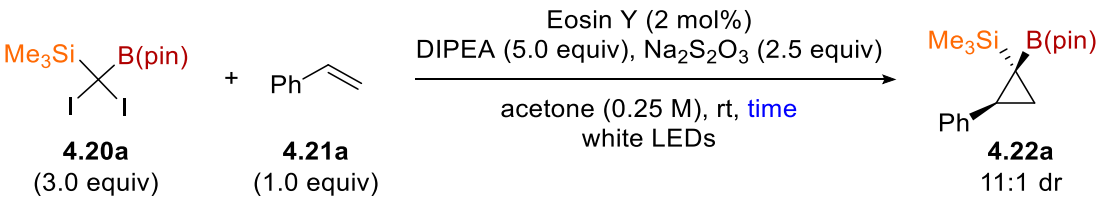
4.20a (3.0 equiv) + **4.21a** (1.0 equiv) → **4.22a** 11:1 dr

Entry	Molarity (M)	Yield 4.22a (%)[a]
1	0.15	71
2	0.25	80
3	0.50	73

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

The effect of reaction time on the borosilylcyclopropanation reaction was investigated (Table 4.9). It was observed that the yield of cyclopropane **4.22a** increased as a function of time until it reached a maximum. For the complete cyclopropanation of styrene, 24 h were required to reach the plateau (entries 1-4). The diastereoselectivity was not affected by the reaction time.

Table 4.9 Effect of the time on the light-mediated borosilylcyclopropanation reaction.



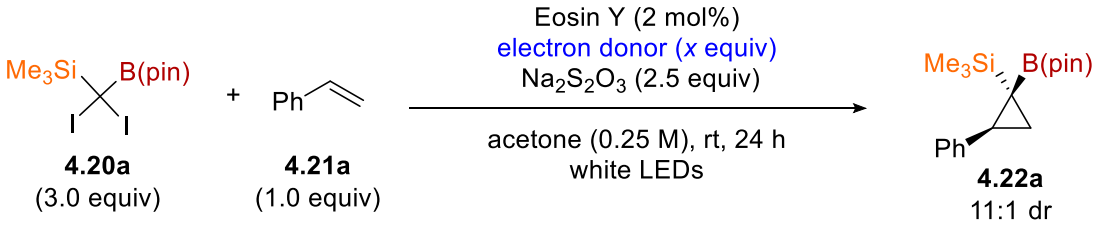
4.20a (3.0 equiv) + **4.21a** (1.0 equiv) → **4.22a** 11:1 dr

Entry	Reaction time (h)	Yield 4.22a (%)[a]
1	12	68
2	16	80
3	20	83
4	24	89
5	48	87

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

Next, we examined whether different electron donors would affect the yield of the borosilylcyclopropanation reaction (Table 4.10). Triethylamine was detrimental for the reaction (entry 2). *n*-Tributylamine gave a slightly decreased yield of cyclopropane **4.22a** when compared to the DIPEA (entry 3). When using triethylamine, pyridine, diethylamine and diisopropylamine, the reaction rate was slow (entries 2 and 4-6). Removal of the electron donor was almost completely detrimental to the reaction (entry 7). Increasing the number of equivalents of the electron donor had no effect on the yield as long as at least 5.0 equivalents were used (entries 1 vs 8 vs 9).

Table 4.10 Effect of the nature and stoichiometry of the electron donor in light-mediated borosilylcyclopropanation reaction.

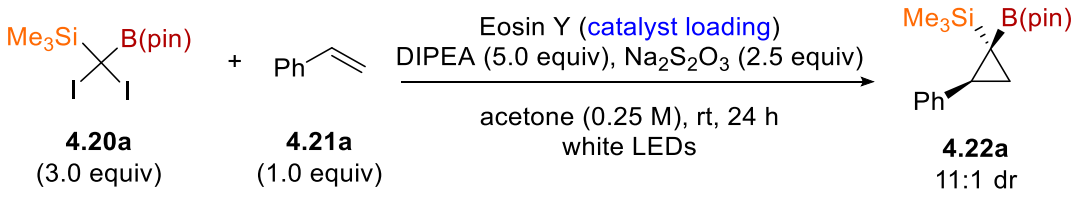


Entry	Electron donor	Equivalents of electron donor (*x*)	Yield 4.22a (%)[a]
1	DIPEA	5.0	89
2	Et_3N	5.0	<5
3	*n*-Bu_3N	5.0	82
4	Pyridine	5.0	<5
5	Et_2NH	5.0	25
6	*i*-$PrNH_2$	5.0	13
7	-	-	11
8	DIPEA	2.5	68
9	DIPEA	10.0	83

[a]Yield of the combined diastereomers determined by ^1H NMR spectroscopy using triphenylmethane as the internal standard.

Evaluation of different catalyst loadings of Eosin Y in the borosilylcyclopropanation (Table 4.11) demonstrated that 2 mol% and 5 mol% afforded the highest yields (entries 2 and 3).

Table 4.11 Optimization of the catalyst loading in the light-mediated borosilylcyclopropanation reaction.



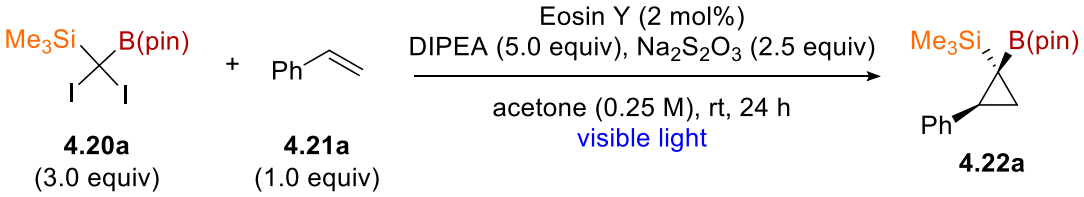
4.20a (3.0 equiv) + **4.21a** (1.0 equiv) → **4.22a** 11:1 dr

Entry	Eosin Y loading (mol%)	Yield 4.22a (%)[a]
1	1	79
2	2	89
3	5	89

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

The last parameter to be optimized was the source of light (Table 4.12). Under the optimized reaction conditions using white LEDs, product **4.22a** was isolated in 81% yield (entry 1). Although the maximum absorbance of Eosin Y is at 520 nm (green region of the electromagnetic spectrum, see Figure 1.16), a lower yield was obtained with the monochromatic green LEDs (entry 2). As expected, lower yields were obtained with blue LEDs or purple LEDs (entries 3 and 4) due to the maximum absorbance of Eosin Y being outside of these monochromatic light wavelengths. Interestingly, while no product was observed in the dark (entry 5), a 60% yield and 10:1 diastereomeric ratio were obtained upon heating at 56 °C in a sealed vessel in the dark (entry 6).

Table 4.12 Optimization of the light source in the light-mediated borosilylcyclopropanation reaction.



4.20a (3.0 equiv) + **4.21a** (1.0 equiv) → **4.22a**

Entry	Light source	λmax (nm)	Yield 4.22a (%)[a]	dr
1	White LEDs	400-700	89 (81)[b]	11:1
2	Green LEDs	520	61	12:1
3	Blue LEDs	450	75	12:1
4	Purple LEDs	380-400	44	12:1
5[c]	-	-	-	-
6[d]	-	-	60	10:1

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [b]Isolated yield. [c]Reaction vessel wrapped in aluminum foil. [d]At 56 °C in a sealed vessel.

The structure and stereochemistry of the white crystalline cyclopropane **4.22a** was unambiguously confirmed by X-ray crystallography (Figure 4.4). As predicted by the bulkiness of the trimethylsilyl substituent, the major diastereomer had the phenyl and the silyl group in a *trans* relationship.

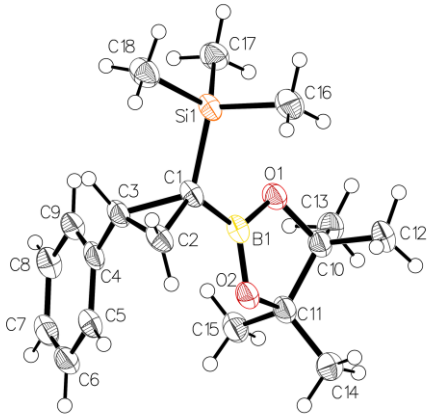


Figure 4.4 X-ray crystallography of borosilylcyclopropane **4.22a**.

4.4.3 Scale-up of the Borosilylcyclopropanation Reaction.

Scaling up the borosilylcyclopropanation reaction of substrate **4.21a** on a 1.0 mmol-scale led to an 80% isolated yield of cyclopropane **4.22a** but it required a longer reaction time (48 h vs 24 h). Figure 4.5 shows the physical appearance of the reaction and product obtained on larger scale.

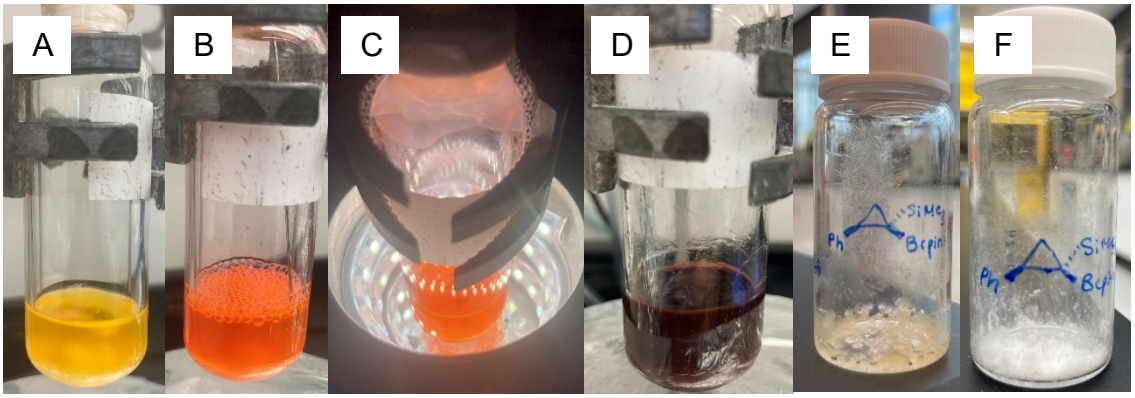


Figure 4.5 Pictures of the reaction mixture of the light-mediated borosilylcyclopropanation reaction.

(A) before the addition of DIPEA, (B) after the addition of DIPEA while degassing, (C) set up, (D) after 40 hours under irradiation, (E) crude mixture, (F) purified cyclopropane **4.22a**.

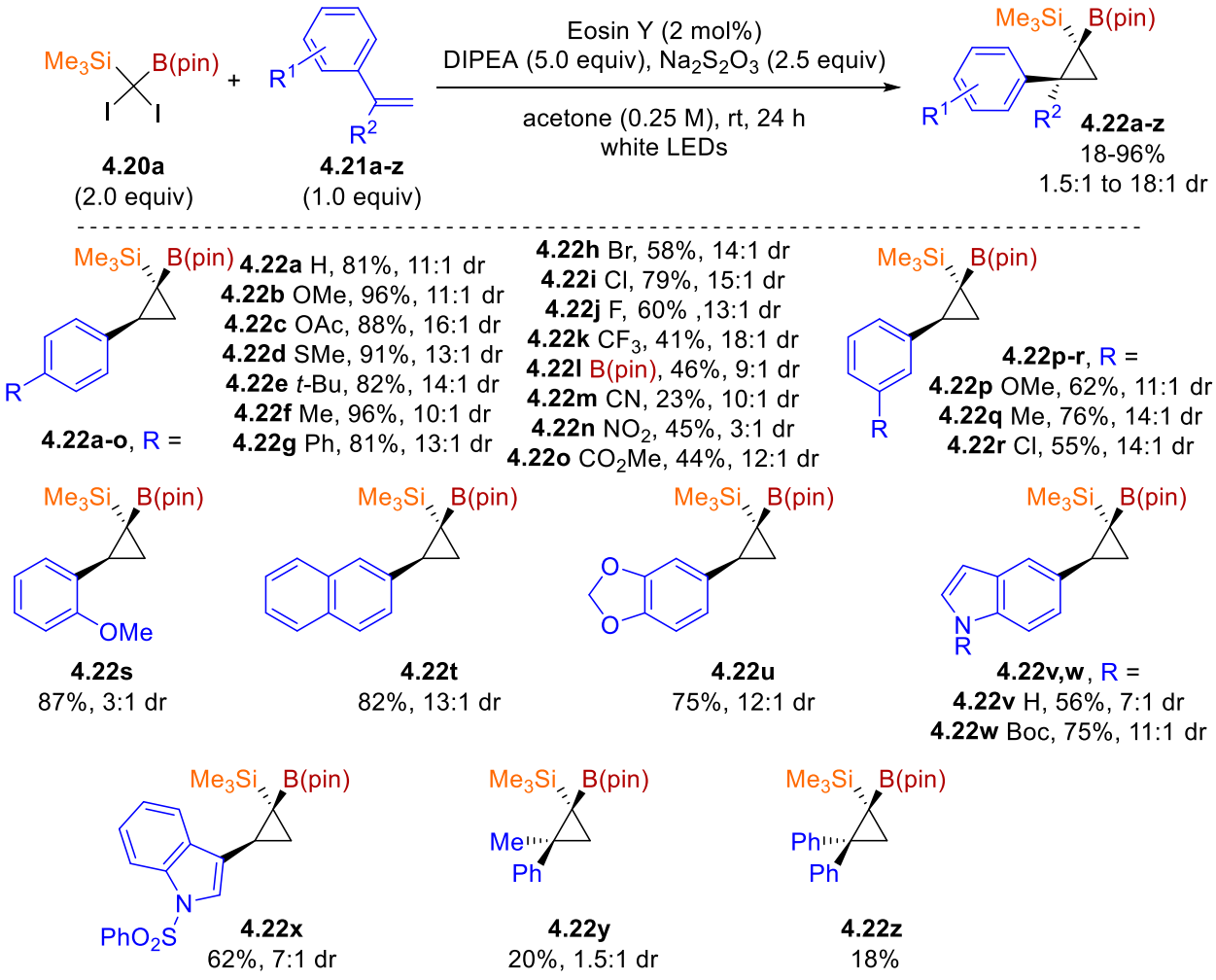
4.5 Scope of the *gem*-Borosilylcyclopropanation Reaction

4.5.1 Cyclopropanation of Substituted Styrene Derivatives

To explore the generality of the reaction, an array of substituted styrenes **4.21a-z** were submitted to visible-light mediated borosilylcyclopropanation (Table 4.13). To decrease the number of equivalents of reagent and facilitate purification, 2.0 equivalents of diiodoboromethylsilane **4.20a** were used instead of 3.0 as determined during optimization studies. Borosilylcyclopropanes **4.22b-m, o-t, x-z** were synthesized by Josiane Perrault-Dufour during an undergraduate summer internship in the Charette group. Borosilylcyclopropanes obtained from electron-rich substituted styrenes (**4.22b–f**) or styrenes bearing a halogen (**4.22h–k**) were obtained in 86–96% yields and excellent diastereoselectivities. Except for **4.22n**, **4.22s** and **4.22y**, diastereomers were inseparable and yields were reported as a mixture of diastereomers. The reaction was compatible with a boronate ester substituent on the styrene moiety as cyclopropane **4.22l** was obtained in 83% yield (determined by ^{1}H NMR) and 46% isolated yield. The bis(boronate

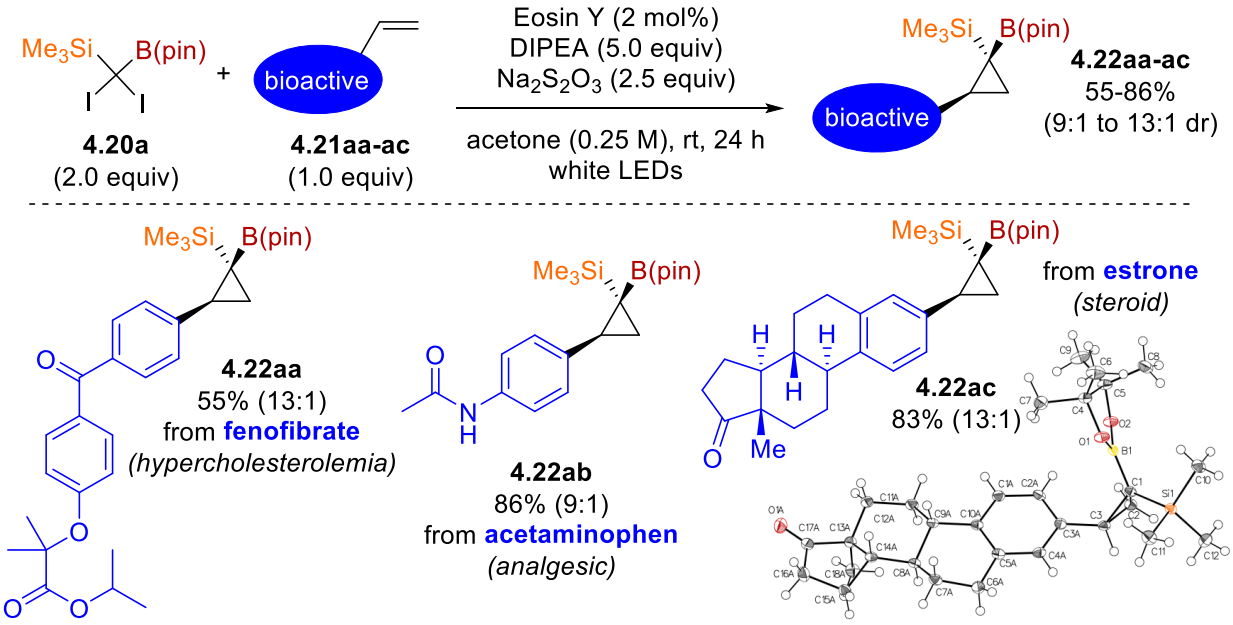
ester) was particularly unstable over silica, and decomposition was observed upon purification. Interestingly, styrenes with strong electron-withdrawing groups were less reactive as the cyclopropanes adorned with *p*-trifluoromethyl **4.22k,** *p*-cyano **4.22m** and *p*-nitro **4.22n** substituents were synthesized in 23–45% yield. Sterically hindered alkenes were well tolerated, and both *o*- and *m*-substituted styrenes delivered products **4.22p-s** in 55–87% yield with modest to excellent diastereoselectivity. Naphthyl- and benzodioxole substituted alkenes provided the desired borosilylcyclopropanes **4.22t** and **4.22u** in 82% and 72% yields respectively. Free or protected indolyl-substituted alkenes were compatible with the reaction conditions and afforded cyclopropanes **4.22v–x** in good yields. 1,1-Disubstituted alkenes were tolerated, albeit tetrasubstituted cyclopropanes **4.22y** and **4.22z** were obtained in moderate yields and low diastereoselectivity (**4.22y**).

Table 4.13 Scope of the visible light-mediated *gem*-borosilylcyclopropanation reaction.



The *gem*-borosilylcyclopropanation reaction can be used for the multi-step, late-stage functionalization of active pharmaceutical ingredients (API) related derivatives (Table 4.14). Alkenes derived from well-established APIs, such as fenofibrate and acetaminophen, and the natural product estrone afforded drug-like molecules **4.22aa-ac** in 55% to 86% yield.

Table 4.14 Late-stage functionalization of API related derivatives using visible light-mediated borosilylcyclopropanation reaction conditions.

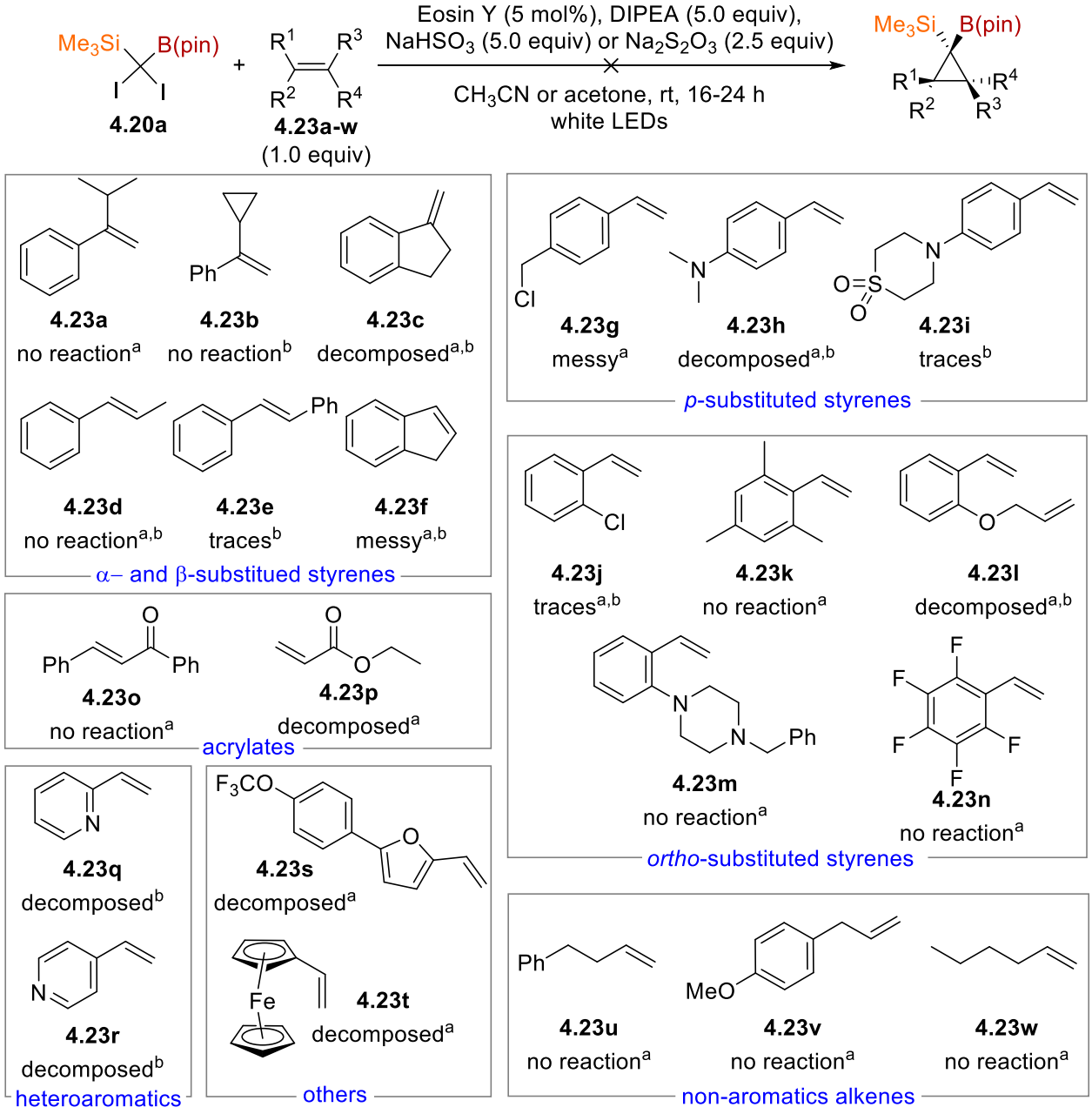


4.5.2 Limitations of the *gem*-Borosilylcyclopropanation

Additional investigations into the scope of the borosilylcyclopropanation reaction were initiated by Dr. Hong Gang during a post-doctoral fellowship in the Charette laboratories. In most cases, reagent **4.20a** was not recovered since it is unstable under reaction conditions. The cleavage of one C–I bond on reagent **4.20a** takes place without the presence of an alkene. Although α-methyl- and α-phenyl styrenes were tolerated under the reaction conditions (Table 4.13, **4.22y** and **4.22z**), α-substituted styrenes **4.23a-c** and β-substituted styrenes **4.23d-e** did not produce the desired products (Table 4.15). No reaction was observed for the cyclopropanation of the α-isopropyl-styrene **4.23a**, β-phenylstyrene **4.23e** and β-methyl styrene **4.23d** as the styrene starting materials were recovered. α-(Cyclopropyl)styrene **4.23b** was similarly too hindered to give the expected bis-cyclopropane and starting materials were recovered quantitatively. For 1-methyleneindane **4.23c**, indene **4.23f**, the corresponding cyclopropanes were not observed in the crude mixture and no

starting material was recovered as well. *p*-(Chloromethyl)styrene **4.23g** and *p*-(1,1-dioxothiomorpholino)styrene **4.23i** led to traces amount of the desired product. Most likely due to its increased basicity, *p*-(dimethylamine)styrene **4.23h** decomposed under reaction conditions. Due to increased steric hindrance, low conversion or no reaction was observed from the borosilylcyclopropanation of *o*-substituted styrenes **4.23j-m**. As observed with electron poor styrenes **4.21m-o**, the low reactivity of 2,3,4,5,6-pentafluorostyrene **4.23n** was likely caused by its poor nucleophilicity. Although the cyclopropanation of chalcone-type substrates using diiodomethane was previously reported (Scheme 1.27),[115] no reaction was observed for the borosilylcyclopropanation of (*E*)-chalcone **4.23o**. In parallel, degradation of ethyl acrylate **4.23p** was observed when it was submitted to borosilylcyclopropanation conditions. Heteroaryl-substituted alkenes were also tested. Unfortunately, due to their increased basicity, *o*-vinylpyridines **4.23q** and *p*-vinylpyridines **4.23r** led to decomposition products and no starting materials were recovered. For furyl-substituted alkene **4.23s** and ferrocenyl-substituted alkene **4.23t**, no desired product was observed as the alkenes decomposed under reaction conditions. Alkyl substituted-alkenes **4.23u-w** did not react under reaction conditions as the alkyl radical.

Table 4.15 Limitations of the visible-light mediated borosilylcyclopropanation reaction.



[a]Conditions A: Reagent **4.20a** (2.5 equiv), $NaHSO_3$ (5.0 equiv), CH_3CN (0.18 M), 18 h.

[b]Conditions B: Reagent **4.20a** (2.0 equiv), $Na_2S_2O_3$ (2.5 equiv), acetone (0.25 M), 24 h.

Our efforts to extend the scope of the methodology prompted us to explore whether alkynes would be suitable starting materials. Phenylacetylene was submitted to *gem*-

borosilylcyclopropanation conditions, aiming to obtain the corresponding borosilylcyclopropene (Figure 4.6).

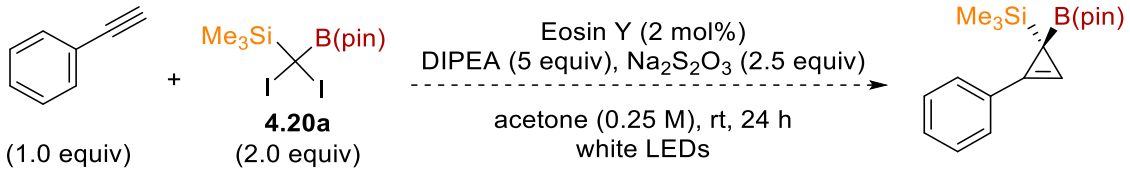


Figure 4.6 Attempt towards borosilylcyclopropenation using visible light-mediated borosilylcyclopropanation optimized conditions.

Although ^{1}H, ^{13}C and ^{11}B NMR spectroscopic spectral data seemed to support the formation of the desired borosilylcyclopropene, high resolution mass spectrometry did not give the expected 314.1873 *m/z*, but rather a 629.3817 *m/z*. While the results correspond to twice the desired value, it was quite unlikely that the product dimerized during the ionization process of the analysis. The product was amenable to X-ray crystallographic analysis that revealed a dimeric 1,3,5-hexatriene **4.24**, with each double bond having *Z*-stereochemistry (Figure 4.7). 1,3,5-Hexatriene **4.24** was isolated in 25% yield.

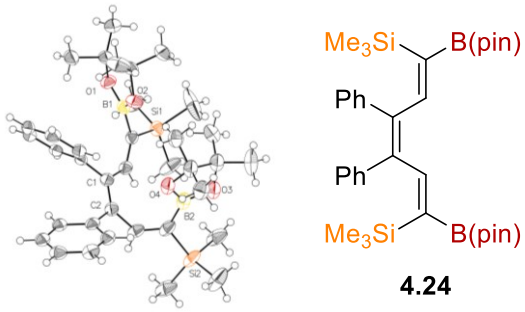


Figure 4.7 X-ray crystallography of the product resulting from attempted borosilylcyclopropenation.

4.6 Postulated Mechanism of the Borosilylcyclopropanation.

The first reaction mechanism investigated was the possibility of a radical chain process. The borosilylcyclopropanation of styrene was irradiated with white LEDs for only 60 minutes and then the light was turned off and the reaction vessel was wrapped in aluminum foil and stirred for 23 hours. Under the procedure, only traces amount of the desired cyclopropane **4.22a** were obtained, suggesting that a radical chain process was not in effect.

The $E^{Red}½_{(\mathbf{4.20a})}$ = –1.28 V vs saturated calomel electrode (SCE) redox potential of borosilyldiiodomethane **4.20a** was previously determined by Sayes.[169] A mechanism could be proposed according to the redox potentials of **4.20a**, Eosin Y (EY) and DIPEA ($E^{Ox}½_{(DIPEA)}$= +0.63 V vs SCE) (Figure 4.8).[169] A reductive quenching cycle was excluded since Eosin Y in its ground state is not able to oxidize diiodoboromethylsilane **4.20a** ($E^{Red}½_{(EY)}$ = –1.08 V vs SCE compared to $E^{Red}½$(**4.20a**)= –1.28 V vs SCE).[101]

As such, an oxidative quenching cycle with Eosin Y was postulated. Upon visible-light irradiation, the excited state of Eosin Y is oxidized by diiodoboromethylsilane **4.20a** leading to a transient radical anion that fragments into an iodo-boromethylsilane radical. The ground state of Eosin Y is recovered upon reduction by DIPEA to restart the catalytic cycle. Electron donors having higher redox potentials could theoretically no be able to regenerate Eosin Y.

Following SET from the photocatalytic cycle, radical addition of the resulting fragmented iodo-boromethylsilane radical **4.20a'** on styrene **4.21a** gives benzylic radical intermediate **4.25**, which would undergo ring closure to obtain cyclopropane **4.22a**. Based on this proposed mechanism, unstabilized radicals resulting from alkene **4.23u-w** could not provide the corresponding cyclopropane. Remaining iodide radical could be reduced by DIPEA or its corresponding radical cation. The subsequent cyclopropanation step could take place via either anionic or radical pathway.

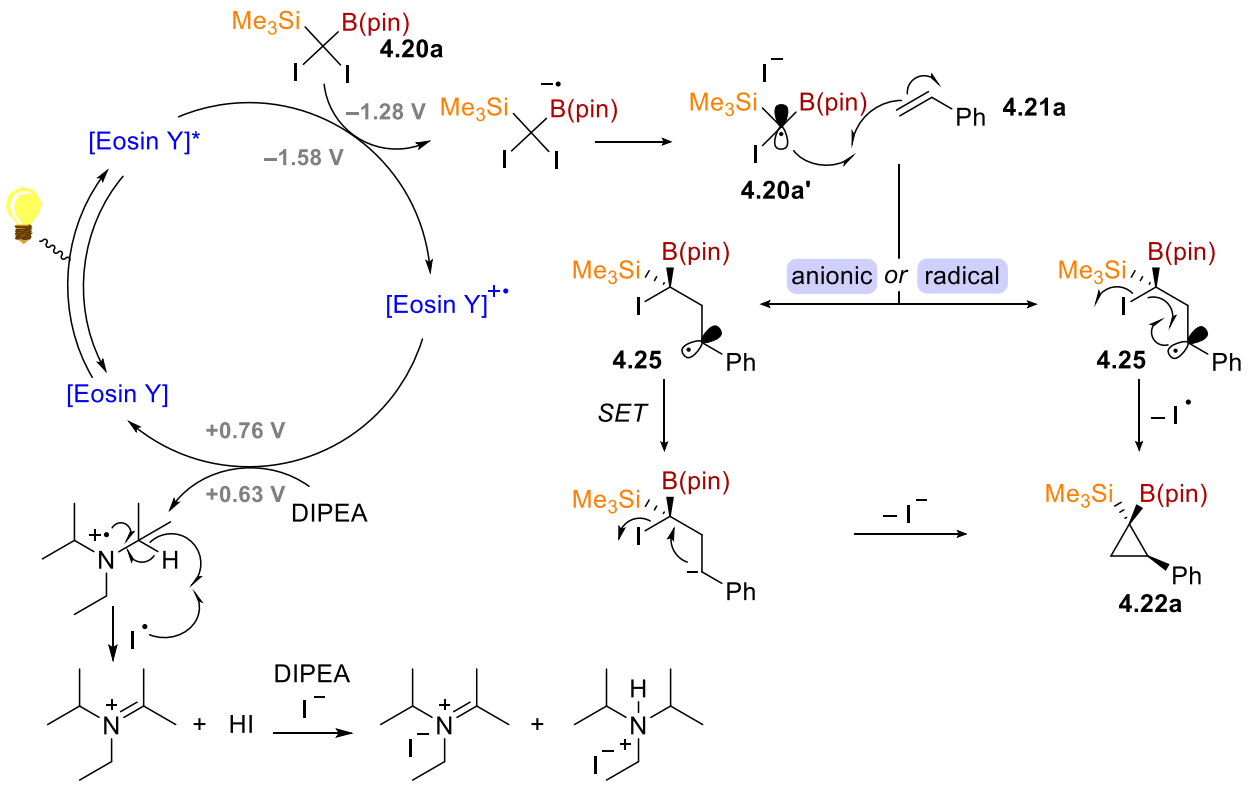


Figure 4.8 Postulated catalytic cycle of the visible light-mediated borosilylcyclopropanation reaction.

To elucidate whether the stereo-determining cyclopropanation step was anionic or radical, computational studies, were conducted by Lucille Wells in Pr. Marisa Koslowski's group at the University of Pennsylvania. To simplify the calculations, the pinacolic methyl groups were replaced with hydrogens. It was calculated that the barrier of the anionic pathway was 7.9 kcal/mol lower than the barrier of the radical pathway and a mechanistic proposal for the cyclopropanation step was put forth (Figure 4.9). Radical **4.25** goes through a single electron transfer with Eosin Y to give a benzylic anion. The species rapidly cyclizes to the four-membered ring intermediate **4.26**. Finally, a concerted 1,2-migration driven by the boron atom and expulsion of iodide give the single diastereomer **4.22a**. Hence, likely due to the stabilization of the carbanion by the boron atom, the anionic pathway appears to be predominant. Adding an electron-withdrawing group on the aromatic ring decreases the free energy of the benzylic anion intermediate, thereby increasing the activation energy of the subsequent cyclization step. With added stabilization, the acyclic benzylic anion might be longer lived and free rotation of the chain could lead to an increased amount of the

minor diastereomer, providing a possible explanation for the lower yields and diastereoselectivities observed during cyclopropanation of electron-poor styrenes (**4.22k**, **4.22m** and **4.22n**).

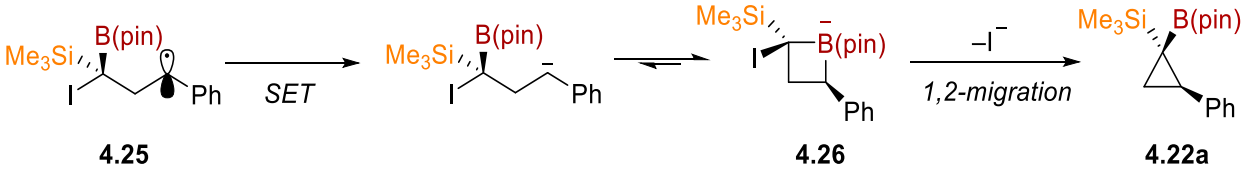
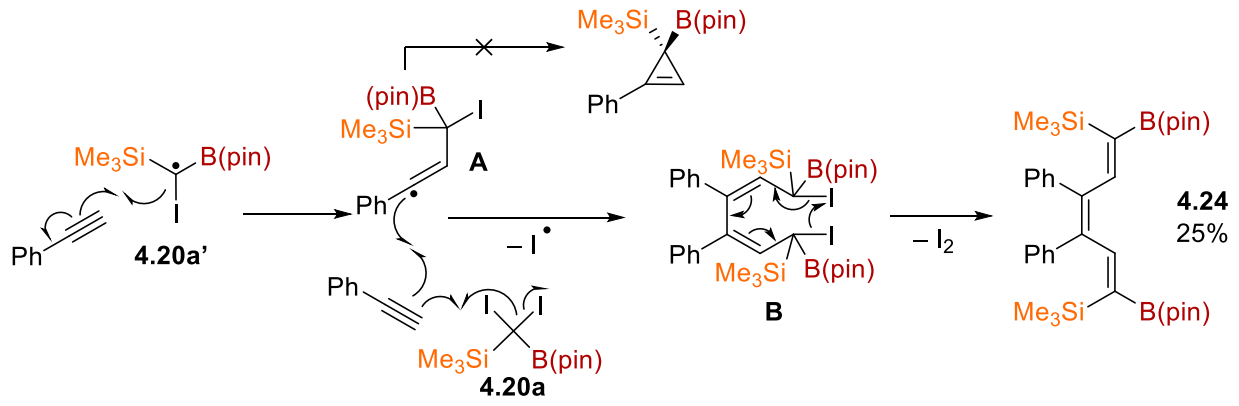


Figure 4.9 Visible light-mediated *gem*-borosilylcyclopropanation cyclization step mechanism

A mechanism for the formation of hexatriene **4.24** was proposed and is depicted (Scheme 4.11). Starting from radical **4.20a'** created by the photocatalytic cycle previously presented, a radical addition of phenylacetylene would occur to give phenyl-stabilized radical **A**. Unfortunately, the radical did not go through cyclization as desired, most likely due to the high energy of the strained cyclopropene. Radical **A** could react with another phenylacetylene molecule. The resulting species could then react with another molecule of **4.20a** in a S_N2 fashion while expelling one iodine radical, which is terminated by SET from DIPEA to its radical cation. The resulting dimeric intermediate **B** would go through a concerted expulsion of iodine to generate triene **4.24** stereoselectively.



Scheme 4.11 Postulated mechanism for the formation of the 1,3,5-hexatriene product **4.24.**

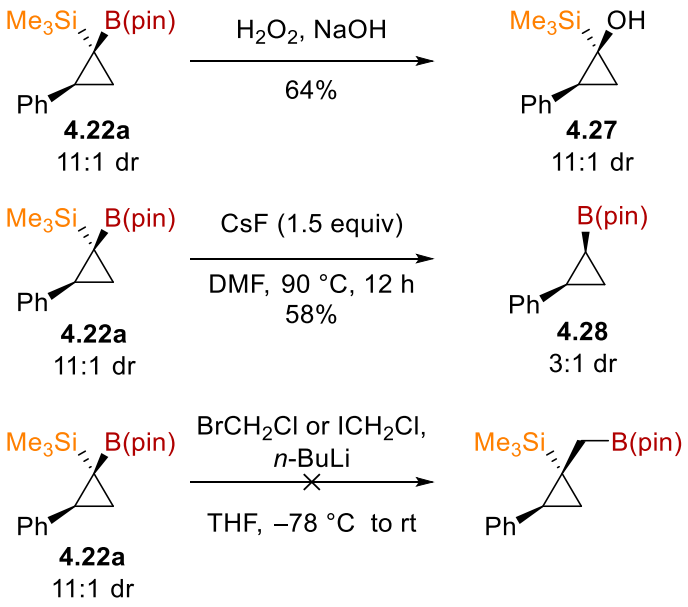
4.7 Synthetic Applications of *gem*-Borosilylcyclopropanes

To further demonstrate the synthetic utility of *gem*-borosilylcyclopropanes, cyclopropane **4.22a** as a 11:1 mixture of diastereomers was submitted to various post-functionalization reactions to produce functionalized 1,1,2-trisubstituted or 1,2-disubstituted cyclopropanes. Preliminary

results obtained by Dr. Hong Gang will be presented, followed by the functionalization of the silyl group, then of the boronate group.

4.7.1 Preliminary Functionalization of *gem*-Borosilylcyclopropanes

The boronate ester of cyclopropane **4.22a** could be oxidized to the corresponding alcohol to afford highly valuable 1-silylcyclopropan-1-ol **4.27** in an isolated 64% yield and 11:1 dr (Scheme 4.12). A proto-desilylation of cyclopropane **4.22a** could take place upon treatment with cesium fluoride in DMF to give the borocyclopropane **4.28** in a 3:1 *cis*:*trans* ratio of diastereomers. Preliminary experiments towards Matteson homologation of cyclopropane **4.22a** were unsuccessful and only starting material was recovered. However, the reaction was not monitored by ^{11}B NMR to ensure that the boron ate complex was formed under the conditions.



Scheme 4.12 Preliminary functionalization of *gem*-borosilylcyclopropane **4.22a** by Gang.

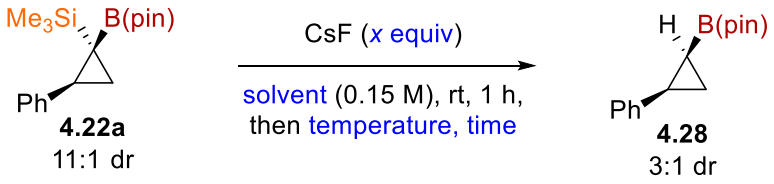
4.7.2 Exploiting the Silyl Functionality for Diversification

Silanes are well known for their use as protecting groups for alcohols that tolerate a wide range of reagents. In the following section, the reactions involving the cleavage of the C–Si bond of cyclopropane **4.22a** will be presented.

Our first goal was to further optimize the proto-desilylation reaction developed by Dr. Hong Gang to improve the diastereoselectivity (Table 4.16, entry 1). The transformation would

complement *trans*-selective methods that were recently reported by our research group.[88,120] A control experiment by removing cesium fluoride to test the thermal stability of **4.22a** was conducted. As anticipated, **4.22a** was stable under thermal conditions, since 98% of starting material **4.22a** was recovered upon heating to 150 °C for 65 h (entry 2). The next step to improve the desilylation of cyclopropane **4.22a** was to do a temperature screening (entries 3-5) in the presence of 5.0 equivalents of cesium fluoride to optimize product formation and diastereoselectivity. No desired product **4.28** was obtained when the reaction was run between 0 and 50 °C. With a possible Hiyama cross-coupling in mind, THF was tested as the solvent. There was no conversion using the conditions (entry 6). The last optimized parameter was the stoichiometry. The large excess of cesium fluoride was reduced to 4.0 equivalents, which led to incomplete conversion (entry 7) while 5.0 equivalents, gave a 58% yield of cyclopropane **4.28** (entry 8). When the temperature was lowered to 80 °C, the yield dropped to 40% (entry 9). The ratio of diastereomers was similar in all cases (entries 1, 7-9). Although a large excess of cesium fluoride was added, proto-deboration was not observed at 80 °C (entry 9).

Table 4.16 Silyl reduction of borosilylcyclopropane **4.22a** to borocyclopropane **4.28**.

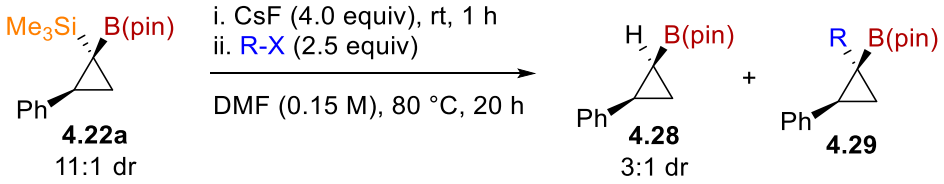


Entry	Equiv of CsF (*x*)	Solvent	Temperature (°C)	Time (h)	Yield	
					4.22a (%)[a]	4.28 (%)[a]
1[b]	9.0	DMF	90	18	-	58
2	-	DMF	150	65	98	-
3	9.0	DMF	0	1	95	-
4	9.0	DMF	25	18	70	< 5
5	9.0	DMF	50	18	92	< 5
6	9.0	THF	50	18	86	-
7	4.0	DMF	90	18	11	33
8	5.0	DMF	90	18	-	58
9	5.0	DMF	80	18	-	40

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [b]Entry done by Dr Hong Gang.

Since the silyl functionality could undergo protonolysis, we hypothesized that it could act as a nucleophile and undergo nucleophilic substitution reactions. Substitution using some electrophiles was attempted (Table 4.17). The addition of *n*-pentyl iodide as the electrophile did not supply any of the desired trisubstituted cyclopropane **4.29**, and the reduced product **4.28** was obtained instead (entries 1 and 2). The addition of benzyl bromide led to traces of the corresponding desired product as observed by crude ^{1}H NMR analysis. Due to the poor yield and small difference in retention factors on silica gel with the starting material, the pure product could not be isolated.

Table 4.17 Substitution of silyl group on borosilylcyclopropane **4.22**.

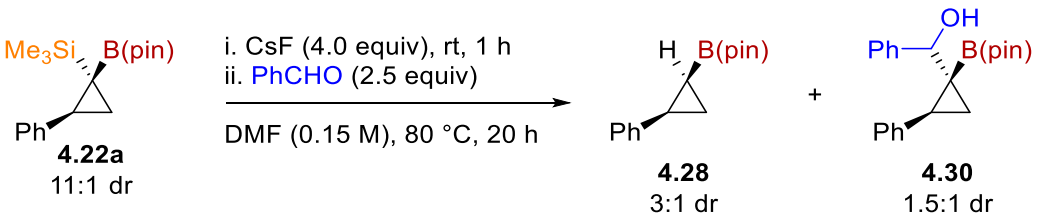


Entry	R	X	Yield		
			4.22a (%)[a]	4.28 (%)[a]	4.29 (%)[a]
1	D	OD	-	53	-
2	*n*-C_5H_{11}	I	25	14	-
3	Bn	Br	27	25	4

[a]Yield of the combined diastereomers (if applicable) determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

A more facile nucleophilic substitution reaction was targeted next. When benzaldehyde was added as the electrophile, the desired product **4.30** was isolated in 48% (Table 4.18, entry 1). Cesium fluoride had to be dried at high temperature under vacuum and stored in the glovebox prior to use and rigorously dried anhydrous solvent must be used to avoid the formation of the proto-desilylated product **4.28** (entry 2). Changing the order of addition of cesium fluoride and benzaldehyde did not improve the yield (entry 3). Quite interestingly, only two diastereomers (out of four possibilities) were formed in a 1.5:1 ratio.

Table 4.18 Reaction of borosilylcyclopropane **4.22a** with benzaldehyde in the presence of CsF.



Entry	Yield		
	4.22a (%)[a]	**4.28 (%)[a]**	**4.30 (%)[a]**
1	-	-	48[b]
2[c]	-	42	-
3[d]	19	28	31[b]

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [b]Isolated yield. [c]Using undried CsF. [d]CsF added after benzaldehyde

To determine whether the two diastereomers of cyclopropane **4.30** arose from a mixture at the benzylic alcohol position or from epimerization of the carbon atom of the cyclopropane, the benzylic alcohol **4.30** was oxidized to the corresponding ketone **4.31** (Scheme 4.13). Under Swern conditions, the resulting single cyclopropyl diastereomer confirmed that the ratio of diastereomers arose from the benzylic chiral center and the configuration of the cyclopropyl carbon remained unaltered.

Scheme 4.13 Oxidation of phenyl-(2-phenylcyclopropyl)methanol **4.30** to acyl cyclopropane **4.30.**

4.7.3 Diversification on the Boronate Functionality

Although boronate esters are useful building blocks, it was anticipated that the bulkiness around the boronate ester in cyclopropane **4.22a** may hamper its reactivity. Hence, reactions that

were specifically designed towards tertiary or sterically hindered boronate esters were attempted using borosilylcyclopropane **4.22a**. Direct aminations are usually conducted on more activate boronates, such as dichloroboranes, difluoroboranes, dialkylborinates, or trialkylboranes, as starting materials. Direct amination conditions of pinacol boronate esters were previously underexplored. In 2019, Pr. Moken's group developed direct amination conditions for boronates to provide the corresponding free amine with retention of stereochemistry (Figure 4.10).[174] To form the tetravalent boron "ate" complex intermediate, an excess of potassium *t*-butoxide was required for reaction with methoxyamine. A subsequent 1,2-migration along with the expulsion of methoxide as the leaving group provided the desired free amine. For highly hindered boronate substrates, the "ate" complex was believed to degrade before 1,2-migration, leading to a deboronated product.

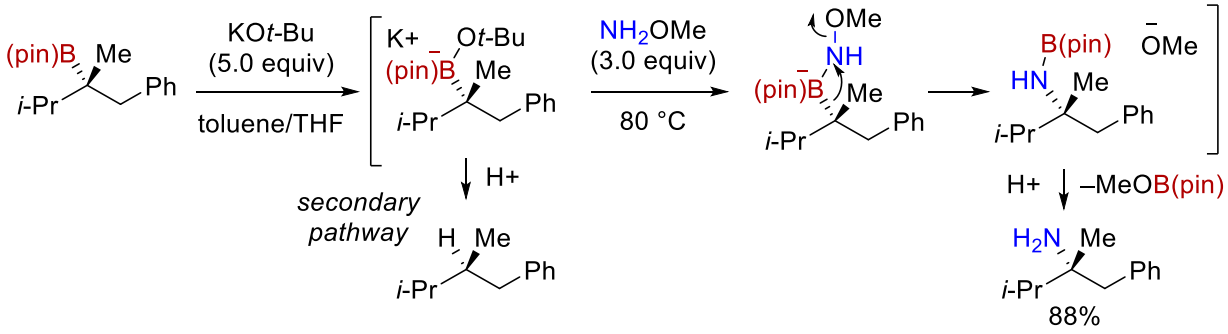
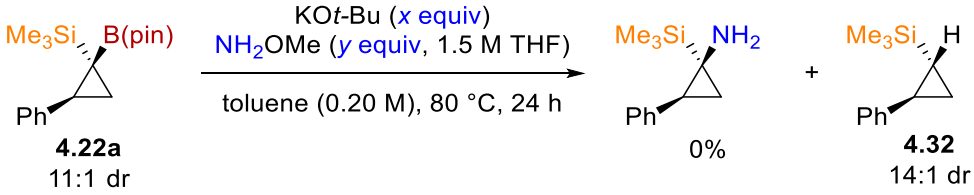


Figure 4.10 Mechanism of direct amination of a tertiary alkylboronic ester.

The conditions developed by Morken for direct amination were applied to borosilylcyclopropane **4.22a** (Table 4.19). No desired cyclopropylamine was observed even when Boc anhydride was subsequently added in a one-pot process to anhydride to facilitate the isolation of the product (entry 1). Reduced cyclopropane **4.32** obtained under the direct amination conditions was also observed in the absence of methoxyamine (Table 4.19, entry 2). The reaction proceeded with very little epimerization thus producing preferentially the *trans* isomer in a 14:1 diastereomeric ratio. Since traces of starting material **4.22a** was recovered with 5.0 equivalents of potassium *t*-butoxide, the stoichiometry was increased to 8.0 equivalents (entry 3). An increased 40% of silylcyclopropane **4.32** was obtained. Control experiments were undertaken, revealing that when the reaction was run at room temperature with 8.0 equivalents of potassium *t*-butoxide (entry 4) or heated to 80 °C in the absence of potassium *t*-butoxide (entry 5) only starting material was recovered.

Table 4.19 Amination on *gem*-borosilylcyclopropane **4.22a** using NH_2OMe as amination reagent.

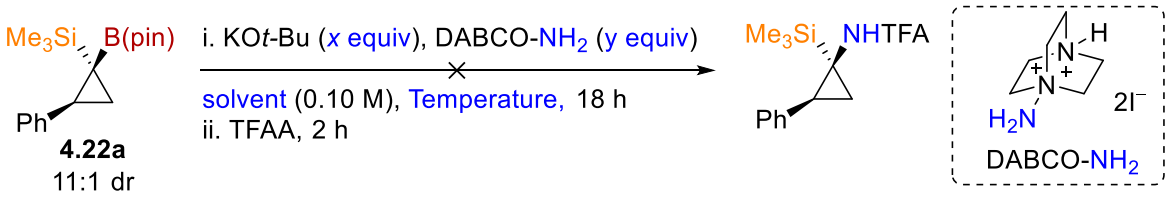


Entry	Equiv of KOt-Bu (*x*)	Equiv of NH_2OMe (*y*)	Yield 4.32 (%)[a]
1	5.0	3.0	25
2	5.0	-	35
3	8.0	-	40
4[b]	8.0	-	-
5[c]	-	-	-

[a]Determined by ^1H NMR spectroscopy using triphenylmethane as the internal standard. [b]Entry completed at room temperature. [c]In refluxing toluene.

An aminoazanium derived from 1,4-diazabicyclo[2.2.2]octane (DABCO) was reported as a solution to aminate sterically hindered pinacol boronates.[175] The reported process used fewer equivalents of potassium *t*-butoxide. Trifluoroacetic anhydride (TFAA) was subsequently added in a one-pot procedure to generate an amide, which is generally easier to isolate. The method was applied to borosilylcyclopropane **4.22a** and unfortunately silylcyclopropane **4.32** was the only observed product (Table 4.20).

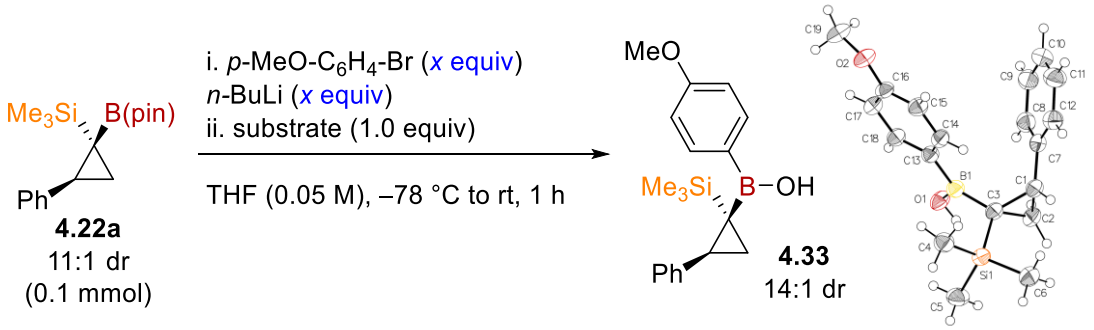
Table 4.20 Amination on *gem*-borosilylcyclopropane **4.22a** using DABCO-NH_2 as amination reagent.



Entry	Equiv of KO*t*-Bu (*x*)	Equiv of DABCO-NH_2 (*y*)	Solvent	Temperature (°C)
1	2.4	1.0	THF	90
2	2.4	1.0	DMF	150
3	20.0	2.0	THF	90

Another functionalization of borosilylcyclopropane derivatives is their reaction with organolithium reagents to produce borinic acids, such as **4.33**. The reaction of cyclopropane **4.22a** to borinic acid **4.33** required a substantial amount of organolithium reagent (Table 4.21). It was concluded that 3.1 equivalents of aryllithium (entries 1-4) allowed isolation of borinic acid **4.33** in 94% yield on a 0.5-mmol scale (entry 5). Borinic acid **4.33** displayed a ^{11}B NMR chemical shift of –3.48 ppm. The structure was unambiguously assigned by X-ray crystallography. Unlike other known cyclopropylborinic acids that are prone to oxidation in the presence of oxygen and air,[86] the cyclopropane **4.33** was an air-stable compound that could be chromatographed on silica gel.

Table 4.21 Synthesis of a borinic acid from borosilylcyclopropane **4.22a**.



Entry	Equiv of 4-MeO-C_6H_4-Li (*x*)	Yield	
		4.22a (%)[a]	4.33 (%)[a]
1	1.1	92	5
2	2.1	37	60
3	3.1	6	80
4	4.1	-	79
5[b]	3.1	-	94[c]

[a]Determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

[b]0.5 mmol scale. [c]Isolated yield.

Inspired by the ease of formation of the ate complex **4.33** by reaction of borosilylcyclopropanes and organolithium reagents, we next examined the potential use of borosilylcyclopropane **4.22a** in the Zweifel olefination.[22] The Zweifel olefination, being a type of transition-metal-free coupling, allows for coupling of boronate esters and a sp^2 nucleophilic center typically obtained from organomagnesium or organolithium reagents. Upon addition of the organometallic species to the boronate ester, the reaction proceeds by activation of the π bond with iodine to form a zwitterionic iodonium intermediate (Figure 4.11). The intermediate undergoes a stereospecific 1,2-metalate rearrangement resulting in the formation of a β-iodoborinic acid, followed by *anti* elimination to afford the resulting *Z*-alkene product if applicable.

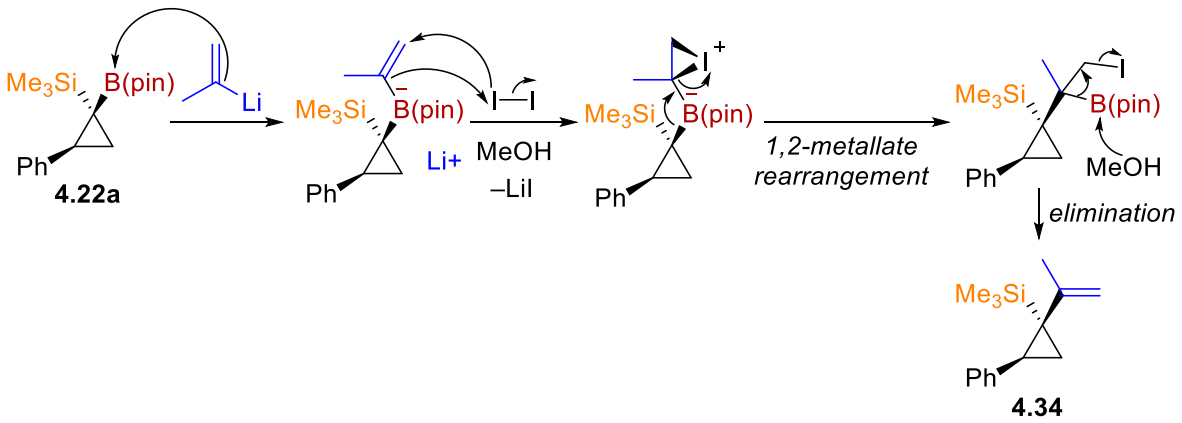
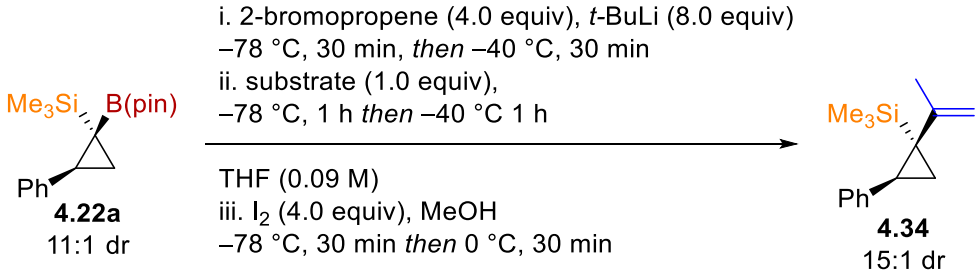


Figure 4.11 Proposed Zweifel olefination of borosilylcyclopropane **4.22a**.

The conditions developed by Aggarwal for Zweifel olefination were applied to borosilylcyclopropane **4.22a** and 2-lithiopropene (Table 4.22).[176] A promising 72% of *gem*-vinylsilylcyclopropane **4.34** was obtained as a single diastereomer on small scale (entry 1). The yield improved to 87% on a 0.5-mmol scale (entry 2).

Table 4.22 Zweifel olefination on borosilylcyclopropane **4.22a**.



Entry	Scale (mmol)	Yield 4.34 (%)[a]
1	0.13	72
2	0.50	87

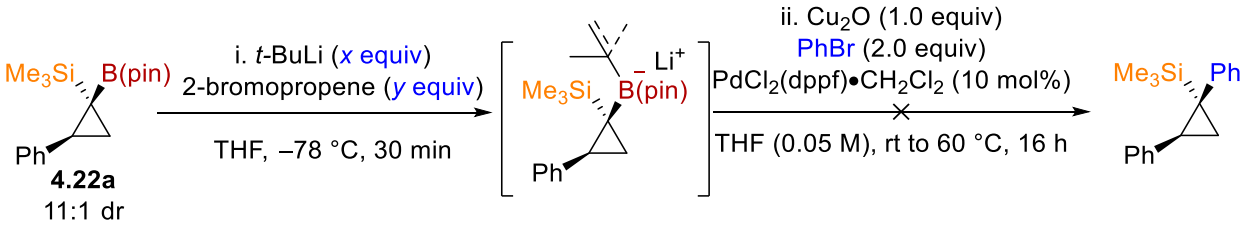
[a]Isolated yield.

4.7.3.1 Palladium-catalyzed Cross Coupling Reactions

Borosilylcyclopropane **4.22a** had resisted Suzuki-Miyaura cross-coupling conditions specifically developed for bulky cyclopropylboronates. As such, we considered related Suzuki-Miyaura cross-couplings conditions on 1-boro-3-silylbicyclo[1.1.1]pentane reported in 2020.[177] To address the sluggish nature of the transmetalation on sterically hindered tertiary boronic ester, *t*-

butyllithium was added as an activator. The conditions were applied to borosilylcyclopropane **4.22a** (Table 4.23). Unfortunately, only starting material was recovered (entry 1). Since borosilylcyclopropane **4.22a** successfully converted into the Zweifel product **4.34**, we speculated that the Suzuki-Miyaura transformation could be completed with 2-lithiopropene instead, however only starting material was obtained following the initial experiment (entry 2).

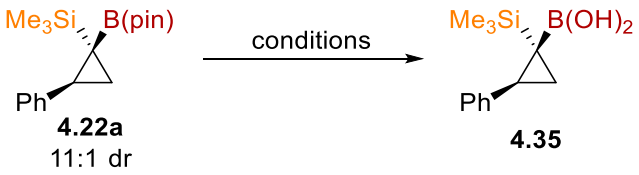
Table 4.23 Preactivated Suzuki-Miyaura cross-coupling using *t*-BuLi on borosilylcyclopropane **4.22a**.



Entry	Equiv of *t*-BuLi (*x*)	Equiv of 2-bromopropene (*y*)
1	2	-
2	8	4

Another possible functionalization of borosilylcyclopropanes could take place via transition-metal free cross-coupling with tosylhydrazones, first reported in 2020.[178] Since the method could tolerate hindered boronic acids such as *t*-butylboronic acid and 1-bicyclo[1.1.1]pentylboronic acid, the conditions seemed optimal for reaction on borosilylcyclopropane **4.22a**. However, the metal-free cross-coupling was successful only on boronic acids, so boronate ester of **4.22a** needed to be deprotected first. Boronate ester **4.22a** was deprotected to the corresponding silylcyclopropylboronic acid **4.35** (Table 4.24). When using concentrated hydrochloric acid with or without sodium periodate and heating to reflux overnight, only starting material was recovered (entries 1 and 2). However, using boron trichloride allowed for the deprotection of the boronate ester in a quantitative yield (entry 3). As the resulting boronic acid was unstable on silica, silylcyclopropylboronic acid **4.35** was used without purification in the next step.

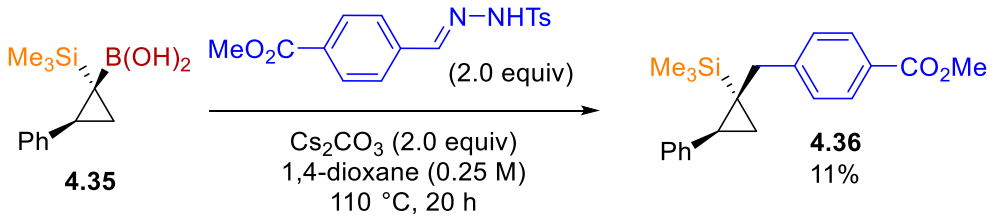
Table 4.24 Deprotection of pinacol boronate ester of cycloporane **4.22a** to boronic acid **4.35**.



Entry	Conditions	Yield 4.35 (%)[a]
1	HCl 12 M, EtOH, 80 °C, 24 h	–
2	$NaIO_4$, HCl 1 M, THF, H_2O, 80 °C, 24 h	–
3	BCl_3, CH_2Cl_2, 45 min, then MeOH	100

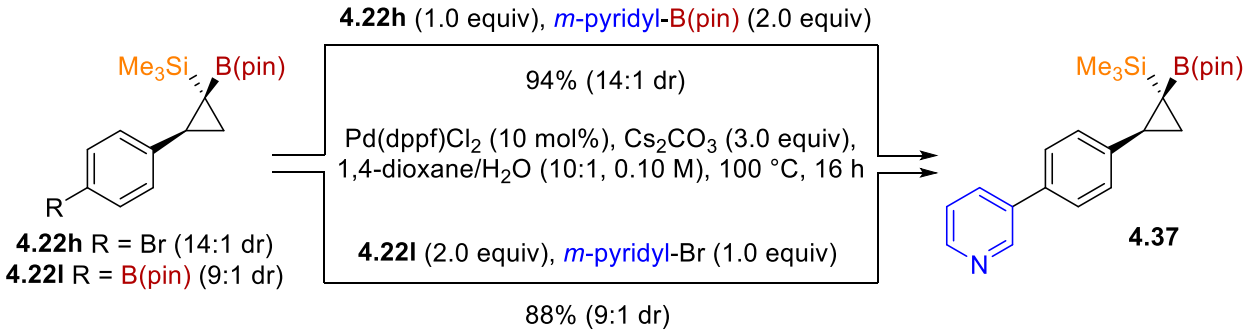
[a]Crude yield.

Under transition metal-free cross-coupling conditions with a tosylhydrazone, silylcyclopropyl boronic acid **4.35** was converted to the coupled adduct **4.36** in an isolated 11% yield as a single diastereomer (Scheme 4.14). In the future, it may be possible to conduct a more extensive optimization of the reaction with tosylhydrazones. Suzuki-Miyaura cross-coupling conditions could be further attempted on cyclopropylboronic acid **4.35**.



Scheme 4.14 Metal-free cross-coupling of *gem*-borosilylcyclopropane **4.35** with a tosylhydrazone.

The robustness of the boronic ester could be taken advantage of to specifically modify a polyfunctional substrate in an orthogonal manner. Indeed, a distal coupling was completed polyfunctionalized cyclopropanes **4.22h** and **4.22l** (Scheme 4.15). When *p*-bromo-phenylborocyclopropane **4.22h** was used as the electrophilic cross-coupling partner and *m*-pyridinylboronate pinacol ester as the nucleophile, the coupled adduct **4.37** was obtained in a 94% yield. Simultaneously, the same set of conditions can be applied using *p*-B(pin)phenylcyclopropane **4.22l** as the nucleophilic partner and *m*-bromopyridine as the electrophilic partner, which furnished the same desired heteroaryl product **4.37** in an 88% isolated yield.



Scheme 4.15 Distal Suzuki-Miyaura cross-coupling of *gem*-borosilylcyclopropanes.

4.8 Conclusion

In summary, a diastereoselective *gem*-borosilylcyclopropanation of a broad scope of styrene derivatives was developed. Metal-free, user-friendly and mild photochemical reaction conditions using acetone as the solvent allowed for the preparation of novel borosilylcyclopropanes. The key reagent used as a starting material in the method was synthesized in a chromatography-free 4-step sequence starting from cheap and readily available commercial reagents. To illustrate the potential of the reaction in late-stage functionalization, 29 borosilylcyclopropanes, three of them being alkyl derivatives from natural or drug-like molecules, were synthesized in up to 96% yield. Complementary to established *trans*-borocyclopropanations, the method produces *cis*-borocyclopropanes. Orthogonal and distal functionalization of borosilylcyclopropanes afforded distinctly valuable synthetic targets and added complexity to existing compounds.

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5. Development of a Catalyst-Free, Microwave-Assisted *gem*-Borosilylcyclopropanation

5.1 Introduction to Microwave-Assisted Chemistry

Applications of high-power microwave energy were discovered in the 1940's. The microwave ovens as we know today started to appear in the 1970's. Since microwave wavelengths are longer than both visible light and infrared light (Figure 1.16), energy from microwaves is not strong enough to break the bonds commonly found in organic molecules. The first uses of microwaves in organic chemistry appeared in 1985.[179]

Microwaves, being a form of electromagnetic radiation, create an oscillating electric field, that causes molecules with a dipole moment to align in parallel with the applied irradiation field creating friction, then heat. Heat energy then arises exclusively from the movement between molecules. Heat in conventional heating (oil bath) is transferred inwards from the outside to the reaction vessel (Figure 5.1). In microwaves, heat is caused by the friction between polar molecules from the inside of the reaction vessel. Moreover, the fact that microwave reactors are sealed and that increasing the temperature simultaneously increases the pressure allow a higher reaction temperature than the boiling point of the solvent.[180] As such, uniform heating at high rates is readily obtained in microwave reaction vessels which can lead to significant rate enhancements and shorter reaction times.[181] The magnitude of heating produced from microwaves depends on the dielectric properties of the molecules, mainly the solvent. Therefore, the choice of solvent is often critical in microwave-assisted organic chemistry. For example, whereas water, DMF or dichloromethane have high dipolar moments and dielectric constants, benzene, toluene, and diethyl ether, have low dipolar moments and dielectric constants, and are inactive under microwaves.[179]

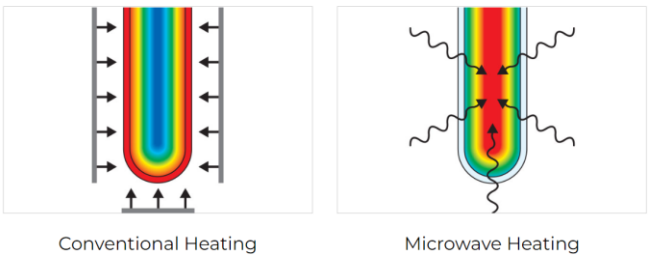
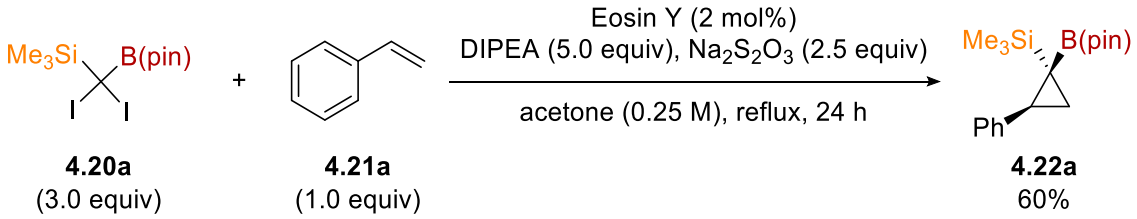


Figure 5.1 Graphical representation of conventional heating vs microwave heating.[182]

5.2 Research Goals

In the preceding chapter, a photochemical synthesis of *gem*-borosilylcyclopropane **4.22a** was presented. During control experiments, it was noted that a 60% yield of the product was obtained when the reaction was run in the absence of light and under refluxing conditions for 24 h in an oil bath (Scheme 5.1).



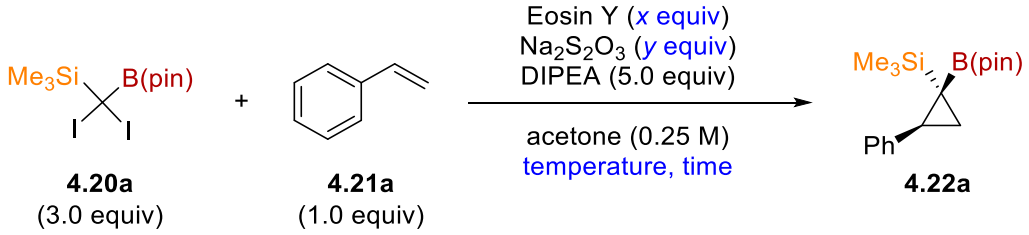
Scheme 5.1 Preliminary result of thermal *gem*-borosilylcyclopropanation.

Encouraged by the possibility of inducing a thermal homolytic cleavage of C–I bonds using microwaves, the following chapter will explore the microwave-assisted synthesis of *gem*-borosilylcyclopropanes as a potential alternative to the parent photochemical process.

5.3 Screening of Reaction Parameters

Cyclopropane **4.22a** was obtained in 60% yield (8:1 ratio of diastereomers) in acetone at 60 °C using a conventional oil bath as the source of heat (Table 5.1, entry 1). Upon microwave irradiation, a 75% NMR yield and a 7:1 dr of the desired product **4.22a** was obtained when heated at 120 °C for 5 hours in acetone (entry 2). As an alternative to acetone, acetonitrile, which has a higher boiling, large dielectric constant, and easily absorbs microwaves, provided cyclopropane **4.22a** as well. Indeed, a 79% NMR yield and an 8:1 dr of the desired product **4.22a** upon microwave irradiation at 120 °C for 5 hours (entry 3). Although the ratio of diastereomers was lower compared to the photochemical conditions, the use of microwave-assisted synthesis removes the need for the catalyst and reducing agent (Figure 4.8).

Table 5.1 Preliminary results of microwave-assisted synthesis of *gem*-borosilylcyclopropane **4.22a**.



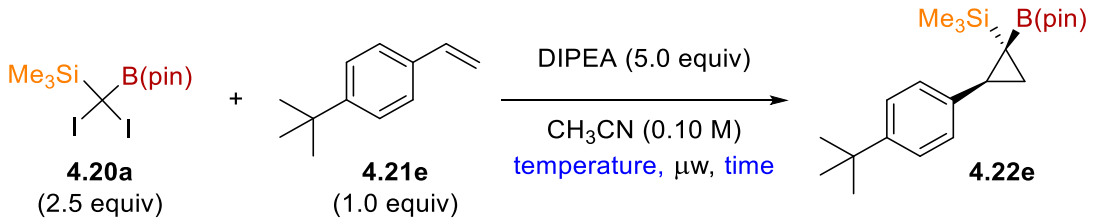
4.20a (3.0 equiv) **4.21a** (1.0 equiv) **4.22a**

Entry	Source of heat	Equiv of Eosin Y (*x*)	Equiv of $Na_2S_2O_3$ (*y*)	Temperature (°C)	Time (h)	Yield 4.22a (%)[a]
1	oil bath	2	2.5	60	24	60
2	microwaves	0	0	120	5	75
3	microwaves	0	0	120	5	79[b]

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [b]Using acetonitrile as the solvent.

During the optimization of previous project in chapter 5, the accurate yield of recovered styrene was difficult to measure considering its volatility and propensity to polymerize. To overcome the volatility problem, *p*-*t*-butyl-styrene **4.21e** was used as the starting material for the following optimization of the microwave assisted protocol. To reach optimal diastereomeric ratios and yields, the temperature and reaction time were studied (Table 5.2). The microwave assisted borosilylcyclopropanation reactions run at lower temperature produced the highest diastereoselectivities but longer reaction times were necessary to maximize the conversions. At temperatures between 120 °C and 150 °C, although the reaction time was reduced, the diastereoselectivity was significantly decreased (entries 1-4). At 100 °C, a 10:1 ratio of diastereomers was observed (entry 5), which is closer to the 11:1 dr obtained under photochemical conditions. The reaction time was studied to conclude that 3 h was the best reaction time (entries 5-7). Decreasing the temperature below 90 °C did not improve the diastereoselectivity and some styrene starting material was recovered (entry 8).

Table 5.2 Effect of temperature and time on the microwave-assisted borosilylcyclopropanation reaction.

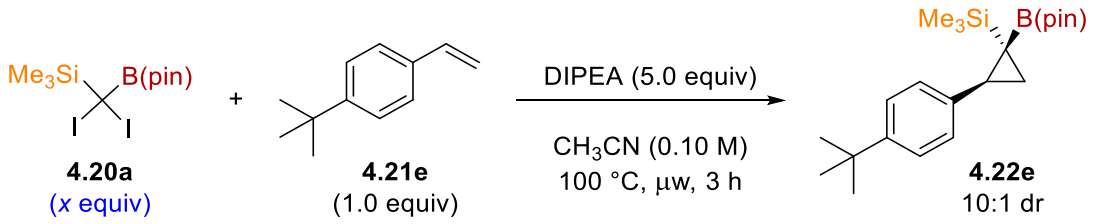


Entry	Temperature (°C)	Time (h)	Yield		dr[b]
			4.21e (%)[a]	4.22e (%)[a]	
1	150	1	18	50	5:1
2	140	2	-	78	7:1
3	120	5	-	81	8:1
4	120	3	2	76	8:1
5	100	5	-	82	10:1
6	100	3	-	81	10:1
7	100	2	14	55	10:1
8	90	4	7	77	10:1

[a]Yield of the combined diastereomers (if applicable) determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [b]Determined by ^{1}H NMR spectroscopy analysis.

Since the diiodomethane reagent **4.20a** is precious, requiring 4 steps to synthesize, attempts were made at reducing the stoichiometry in the borosilylcyclopropanation (Table 5.3). As in previously developed borosilylcyclopropanations (Chapter 4) or borocyclopropanations under photochemical conditions,[120] a large excess of styrene **4.22e** compared to reagent **4.20a** afforded poor conversions (entry 1). Increasing the stoichiometry to 3.0:1.0 slightly decreased the yield of cyclopropane **4.22e** to 75% (entry 4). Similar yields of **4.22e** were obtained when using 2.5 and 3.0 equivalents of reagent **4.20a** (entries 3 and 4). The diastereoselectivity of the borocyclopropanation remained unaffected by the stoichiometric ratio of **4.20a** and **4.21e**.

Table 5.3 Effect of stoichiometry on the microwave assisted borosilylcyclopropanation reaction.

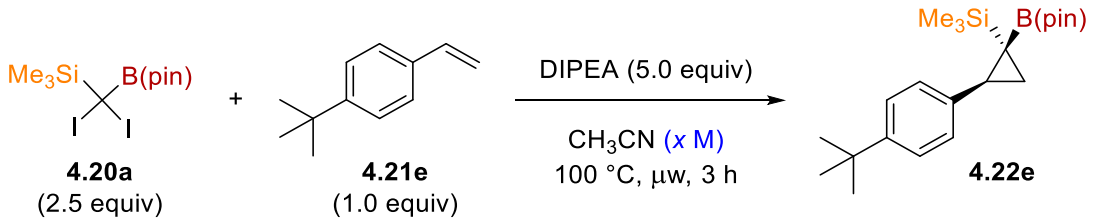


Entry	Equiv of 4.20a (*x*)	Yield	
		4.21e (%)[a]	4.22e (%)[a]
1[b]	1.0	32	3
2	2.0	-	75
3	2.5	-	81
4	3.0	-	75

[a]Yield of the combined diastereomers (if applicable) determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [b]With 5.0 equiv of *t*-Bu-styrene.

Under analogous photochemical conditions, the concentration of the cyclopropanation was a significant parameter, with high concentrations increasing the yield of the reaction. It is important to maintain homogeneity since solids can lead to unequal heating, which can trigger the automatic stop of the instrument.[181] Previous experiments in acetonitrile were conducted at a concentration of 0.10 M since it was the highest concentration at which all the components were soluble. At lower concentrations (Table 5.4, entries 1 and 2), the mixture was homogeneous, but the yield was lower. Since the reactions were conducted on a small scale (0.07 mmol), heterogenous reactions were still submitted to microwave heating. Although higher yields were expected with higher concentrations, it was not the case as similar yields were obtained (entries 3 and 4). Diastereoselectivity increased slightly as the reaction concentration was increased.

Table 5.4 Effect of concentration on the microwave-assisted borosilylcyclopropanation reaction.

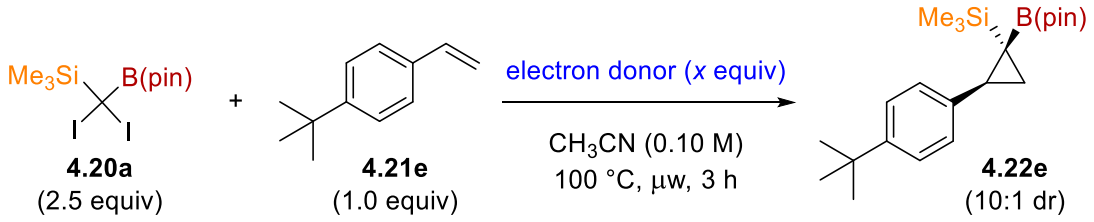


Entry	Concentration (M)	Yield		dr[b]	Soluble
		4.21e	4.22e (%)[a]		
1	0.05	-	73	9:1	Yes
2	0.10	-	81	10:1	Yes
3	0.20	-	77	10:1	No
4	0.30	-	81	11:1	No

[a]Yield of the combined diastereomers determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard. [b]Determined by ^{1}H NMR spectroscopy analysis.

The last parameter to study in the optimization of the microwave assisted borosilylcyclopropanation was the stoichiometry of DIPEA (Table 5.5). Similar yields were obtained with 3.0 to 5.0 equivalents (entry 1-3). With 3.0 equivalents or less, the reaction mixture was initially heterogenous as reagent **4.20a** was partially insoluble. Therefore, 4.0 equivalents were optimal (entry 2) and 71% of the desired product was isolated. As observed under the photochemical conditions (Table 4.4, entry 4), removing DIPEA was completely detrimental to the reaction (entry 6).

Table 5.5 Effect of DIPEA stoichiometry on the microwave-assisted borosilylcyclopropanation reaction.

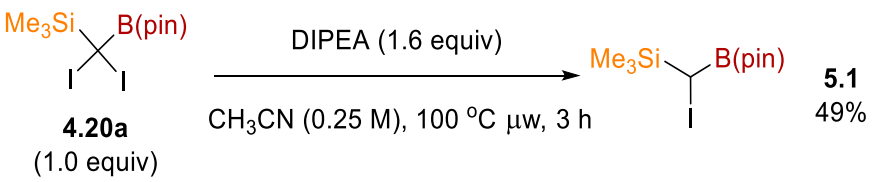


Entry	Electron donor	Equiv of electron donor (*x*)	Yield	
			4.21e (%)[a]	4.22e (%)[a]
1	DIPEA	5.0	-	81
2	DIPEA	4.0	-	78 (71)[b]
3	DIPEA	3.0	2	75
4	DIPEA	2.0	5	60
5	DIPEA	1.0	39	35
6	DIPEA	-	54	-

[a]Yield of the combined diastereomers (if applicable) determined by ^{1}H NMR spectroscopy using triphenylmethane as the internal standard.

5.4 Side Product Formation and Postulated Mechanism

In most cases, *gem*-borosilylcyclopropantion using either photochemical or thermal conditions were very "clean", affording very few side products. In some cases, one by-product was formed in various amounts in crude mixtures of reactions forming borosilylcyclopropanes **4.22a-ac**. The purification of the desired cyclopropanes was hampered by the formation of the side product. Running the reaction without styrene enabled the isolation of side product **5.1** in 49% yield (Scheme 5.2). Since iodine atoms are known to shield ^{13}C and ^{1}H signals,[183] characteristic signals of *C*HIB(pin)SiMe$_3$ at –12.3 ppm and Si(*C*H$_3$)$_3$ at –1.1 ppm in ^{13}C NMR suggested the iodinated monomeric structure of iodomethane **5.1**.



Scheme 5.2 Formation of a side product arising from reagent **4.20a**.

A mechanism for the thermal, microwave assisted protocol was proposed. Upon homolytic cleavage of the C–I bond, radical addition of the resulting fragmented iodo-boromethylsilane radical on styrene **4.21a** provides radical intermediate **4.25**. This species would then undergo a single electron transfer (SET) to obtain the benzylic anion, which is stabilized in the four-membered ring intermediate **4.26**. Upon 1,2-migration of the four-membered ring boronate **4.26** and expulsion of the remaining iodine is obtained cyclopropane **4.22a** (Figure 5.2). Used in excess, DIPEA, which is known to be oxidized by iodine,[184] is crucial for the termination steps of the mechanism.

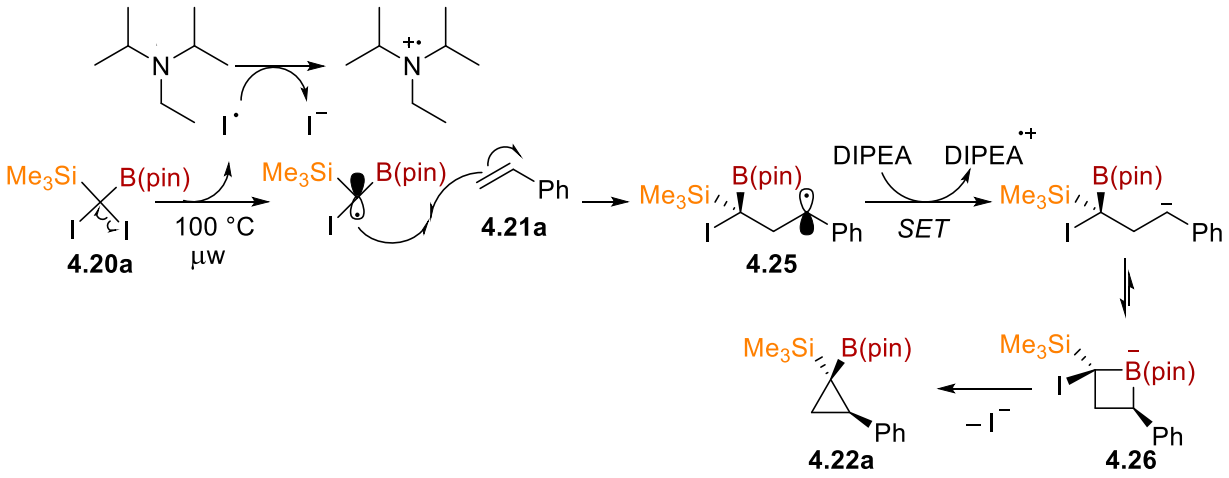


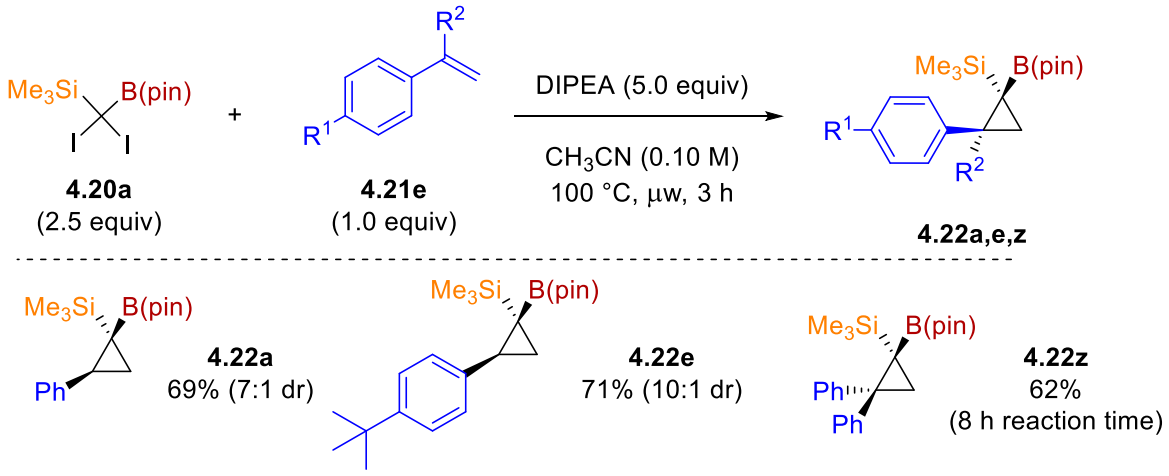
Figure 5.2 Postulated thermal borosilylcyclopropanation reaction mechanism.

5.5 Reaction with Other Substituted Styrenes

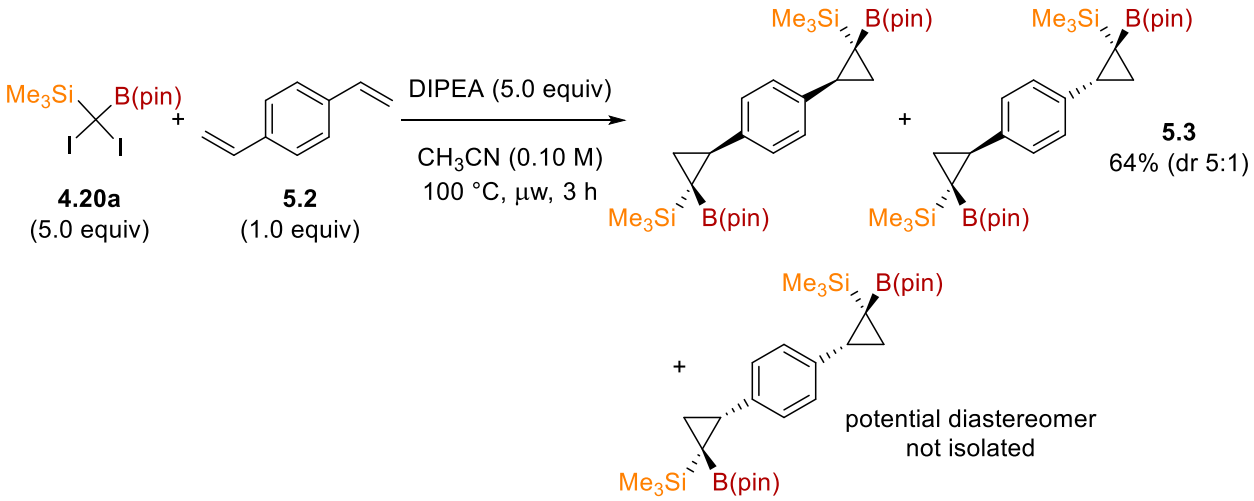
The previously optimized reaction conditions for thermal borosilylcyclopropanation were applied to other styrene derivatives. Styrene itself afforded the desired borosilylcyclopropane **4.22a** in 69% yield and 7:1 dr (Table 5.6). As mentioned previously, the thermal borosilylcyclopropanation of *t*-butyl-styrene provided the desired product **4.22e** in 71% isolated yield along with a 10:1 dr. Although a slightly lower yield than under photochemical conditions was obtained using 4-*t*-butylstyrene, the reaction time was 8-fold shorter. The thermal borosilylcyclopropanation of 1,1-diphenylethylene afforded the desired tetrasubstituted cyclopropane **4.22z** in a 62% isolated yield, which is significantly higher than the 18% yield

obtained under white LED irradiation. The reaction time for **4.22z** was shortened to 8 h as compared to 64 h with previous visible-light mediated conditions.

Table 5.6 Preliminary scope of the microwave-assisted synthesis of *gem*-borosilylcyclopropanes.



Divinylbenzene **5.2**, synthesized in a single step from terephthaldicarboxaldehyde,[185] was submitted to thermal borosilylcyclopropanation conditions to afford the desired 1,4-dicyclopropylbenzene **5.3** in 64% isolated yield and 5:1 dr (Scheme 5.3).



Scheme 5.3 Bis-borosilylcyclopropanation reaction from dicyclopropylbenzene.

5.6 Conclusion

In conclusion, preliminary scope of a microwave-assisted borosilylcyclopropanation of styrene derivatives led to promising results. Microwave-assisted conditions are 8 times more time-

efficient than the previous photocatalyzed conditions. No catalyst, no reducing agent and no light are required. Microwave-assisted synthesis allowed for an alternative to photochemistry. Considering that microwaves reactions are not easily scalable, a related reaction under continuous flow condition is under investigation.

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6. General Conclusion and Perspectives

The research presented in the thesis has described the development of methods for the synthesis of highly substituted cyclopropanes and derivatives, motifs frequently incorporated into drug candidates. Three different methods were elaborated; a diastereoselective zincocyclopropanation towards the synthesis of *cis*-iodocyclopropanes, their cyclization into electron rich 2-substituted bicyclo[1.1.0]butanes, and user-friendly photochemical or microwave-assisted *gem*-borosilylcyclopropanations.

6.1 Zincocyclopropanation using Bromoform as the Carbenoid Source

To access a variety of *cis*-iodocyclopropanes, a streamlined diastereoselective zincocyclopropanation using modified conditions was developed by applying hetero-dihalocarbenoids results recently reported by the Charette group. While previous zincocyclopropanation conditions involved a mixture of the monozinc $XZnCHX_2$ and *gem*-dizinc $(XZn)_2CHX$ carbenoids when using iodoform and ethylzinc iodide, the *gem*-dizinc $(XZn)_2CHI$ carbenoid was exclusively obtained from bromoform and ethylzinc iodide. The zincocyclopropanation reaction concentration was increased 10-fold, reducing the amount of required solvent when using bromoform. The streamlined procedure allowed for improved reaction efficiency. The newly developed conditions, in which half an equivalent of diethylzinc was replaced with a cheaper source of zinc, allowed a significant expansion on the scope of allylic alcohol substrates. *cis*-Iodocyclopropanes were produced in high diastereocontrol and moderate to good yields. Although the scope of the method was limited to free allylic alcohols as the functionality was required for the subsequent project, it would have been interesting to test the method on double-protected allylic alcohols. In the future, it would be interesting to add various electrophiles to the zincocyclopropyl intermediate to provide *cis*–trisubstituted cyclopropanes. Eventually, the functionalization of the cyclopropylmethanol motif on the *p*-methoxybenyzl-cyclopropane followed by the *p*-methoxybenzyl deprotection using recently developed conditions could be investigated (Figure 6.1). An example of chemoselective cyclopropylmethanol functionalization conditions include a cyclopropylmesylate intermediate. The exploration would allow further expansion of the substrate scope and would provide non-benzylated *cis*-cyclopropanes.

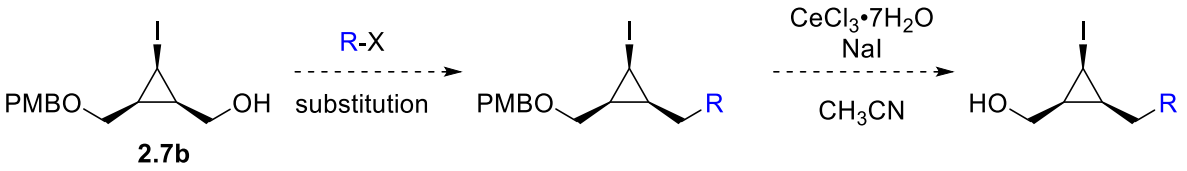


Figure 6.1 Potential further functionalization of *cis*-iodocyclopropane **2.7b**.

6.2 Synthesis and Reactivity of 2-Substituted Bicyclo[1.1.0]butanes

Despite their challenging synthesis, strained small carbobicyclic systems offer interesting reactivity as intermediates in the synthesis of complex molecules. The *cis*-iodocyclopropanes resulting from the first project were used in a straightforward 3-step synthesis of 10 examples of electron rich bicyclo[1.1.0]butanes (BCB) using readily available reagents. As very few antecedents of the derivatives have been reported, the BCBs were functionalized in previously unattainable positions. The underexplored scaffolds exhibited opposite reactivity as compared to previously developed bicyclo[1.1.0]butanes due to their opposite electronic characteristics. Electron rich 2-substituted BCBs were unreactive in various cycloadditions, as well as nucleophilic additions. Conversely, they were reactive towards electrophiles and acidic conditions. It was observed that electron rich 2-substituted BCBs were reactive towards *N*-iodosuccinimide (NIS) or mercury acetate in methanol and diastereoselectively provided substituted cyclobutanes.

In the future, functionalized BCBs such as (bicyclo[1.1.0]butyl)methylamine could be envisaged using the product from the sequence suggested in Figure 6.1. In terms of further BCB post-functionalization, it would be interesting to add different nucleophiles to the reaction mixture after the addition of NIS or $Hg(OAc)_2$ to provide substituted cyclobutanes with diastereocontrol (Figure 6.2a). A similar strategy could be envisioned to build bicyclo[2.1.0]pentanes, commonly called housanes. Upon deprotection of the (*p*-methoxy)benzyl group on iodocyclobutane, the resulting 2-(hydroxymethyl)-1-iodo-3-methoxycyclobutane could be used as a substrate for the mesylation/cyclization sequence (Figure 6.2b). The corresponding bicyclo[2.1.0]pentane, which is also an interesting small strained ring, would be obtained.

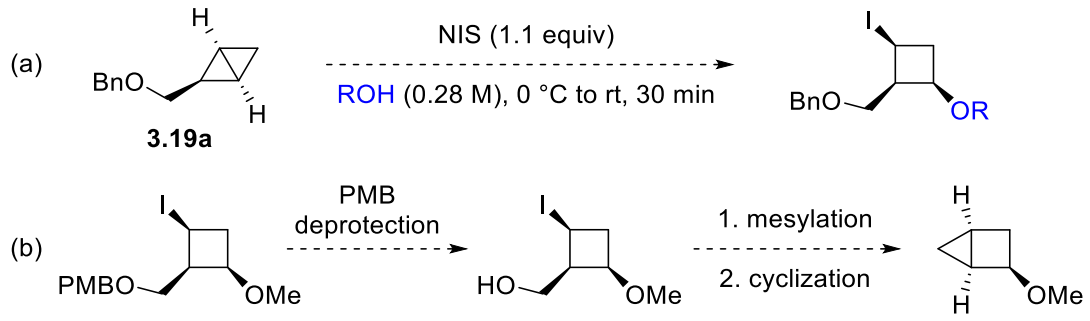


Figure 6.2 Potential synthesis of trisubstituted cyclobutanes and bicyclo[2.1.0]pentane.

6.3 Visible Light-Mediated Borosilylcyclopropanation

Using a diiodosilylmethylboronate carbene precursor, the organic dye-catalyzed, visible-light mediated *gem*-borosilylcyclopropanation of a wide variety of styrene derivatives was developed. The method enabled the preparation of 1,1,2-tri– and 1,1,2,2–tetrasubstituted cyclopropanes in excellent diastereocontrol. To highlight the potential of the reaction in late-stage functionalization, 29 borosilylcyclopropanes, three of them being alkyl derivatives from natural or drug-like molecules, were prepared in up to 96% yield.

The borosilyldiiodomethane key reagent used as the starting material in the method was synthesized in a chromatography-free 4-step sequence starting from cheap and readily available commercial reagents. Since the first two steps of reagent synthesis have similar reaction conditions, it would be interesting to telescope the first two reactions of the reagent synthesis in a one-pot procedure from dichloromethane to prepare boronic acid **4.17a** (Figure 6.3). While the Finkelstein substitution reaction presented drawbacks with regards to the reaction time, the solvent and the temperature, it would be interesting to try the last reaction of the synthesis under mechanochemical solvent-free conditions (Figure 6.3).

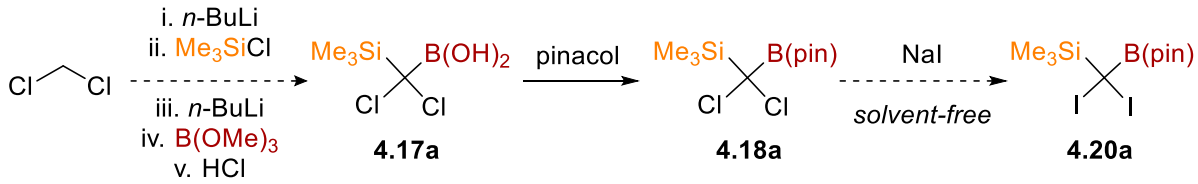


Figure 6.3 Potential streamlined synthesis of borosilyldiiodomethane.

The versatile reactivity of the novel *gem*-borosilylcyclopropanes was demonstrated throughout various post-functionalization reactions. Upon silyl reduction the

borosilylcyclopropanes provided *cis*-borocyclopropanes, which is interesting because other established methods tend to afford *trans*-borocyclopropanes. Orthogonal and distal functionalization of borosilylcyclopropanes afforded distinctly valuable synthetic targets and added complexity to the valuable compounds. In the future, it would be interesting to harness the reactivity of cyclopropylboronic acid **4.35** in Suzuki-Miyuara couplings. With recently developed pinacol ester deprotection conditions, a Suzuki-Miyaura cross-coupling could be next attempted on silylcyclopropylboronic acid **4.35** (Figure 6.4).

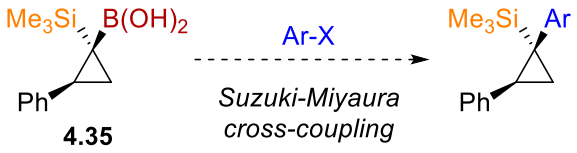


Figure 6.4 Potential Suzuki-Miyaura cross-coupling of cyclopropylboronic acid **4.35.**

6.4 Thermally promoted Borosilylcyclopropanation

A microwave-assisted *gem*-borosilylcyclopropanation was developed. While reaction times were 8 times more efficient than previous photochemical methods, the thermal process did not require a catalyst or reducing agent. Microwave-assisted synthesis allowed for an alternative to photochemistry. While a preliminary thermal borosilylcyclopropanation mechanism was postulated, a radical chain mechanism could be investigated. The preliminary scope of the thermal borosilylcyclopropanation of styrene derivatives led to promising results. The method could be applied to various other styrene derivatives in the future.

Considering that conditions were optimized to be homogenous and that microwaves reactions are not easy to scale, a related reaction under continuous flow conditions is under investigation (Figure 6.5). Continuous flow chemistry is an approach in which a reaction is mechanically pumped into small diameter tubing instead of a static reaction mixture in the regular glassware associated with conventional batch chemistry. Since the tubing surface area is larger compared to conventional flask, flow chemistry generally allows for better heat transfer.

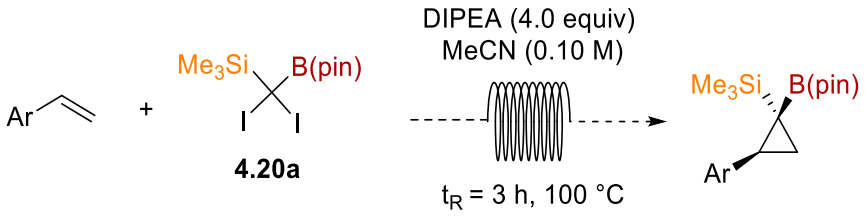


Figure 6.5 Potential thermal borosilylcyclopropanation reaction under continuous flow conditions.

7. Experimental Section

General information: All non-aqueous reactions were run under argon atmosphere with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[186] All glassware was stored in the oven and flame-dried under inert atmosphere prior to use. Flash column chromatography was performed using 230-400 mesh silica (Silicycle) of the indicated solvent system according to standard technique,[187] on silver impregnated silica[188] or on Santai Technologies flash chromatography cartridges on a Sepabean instrument. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by UV light (254 nm), using *p*-anisaldehyde (PA), and/or using ceric ammonium molybdate (CAM) stains. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 400, 500 or 700 MHz spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million with the solvent resonance as the reference $CDCl_3$ (δ = 7.28 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sex = sextuplet, sept = septuplet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million using the central peak of $CDCl_3$ (δ = 77.16 ppm) as the reference. All ^{13}C NMR spectra were recorded on a Bruker Avance 126 or 176 MHz and obtained with complete proton decoupling. All ^{11}B NMR spectra were recorded on a Bruker Avance 101 or 128 MHz. All ^{19}F NMR spectra were recorded on a Bruker Avance 471 MHz. For ^{19}F and ^{11}B NMRs, calibration was performed using a unified scale. All NMR yields were determined using ^{1}H NMR with triphenylmethane as an internal standard. When ambiguous, proton, carbon and stereochemistry assignments were established using HSQC, COSY, NOESY and/or DEPT experiments. Infrared spectra were taken on a Bruker Alpha Platinum ATR (neat) and are reported in reciprocal centimeters (cm^{-1}). High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

Solvents and reagents: Anhydrous, oxygen-free solvents were obtained by distillation. Methanol (MeOH) were freshly distilled over CaH_2. Tetrahydrofuran (THF) was freshly distilled over sodium and benzophenone. Triethylamine (Et_3N) was freshly distilled over potassium hydroxide. Acetone was freshly distilled over calcium sulfate. Diethyl ether (Et_2O) and dichloromethane

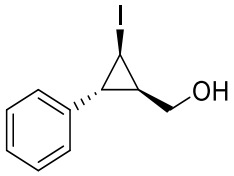
(CH_2Cl_2) were obtained by filtration through drying columns on a filtration system.[189] Unless otherwise stated, commercially available reagents were used as supplied or purified by standard techniques when necessary.[190] *n*-Butyllithium was freshly titrated using recrystallized diphenylacetic acid. Non-commercial starting materials were synthesized according to literature procedures unless otherwise noted. Zinc iodide was purchased from Alfa Aesar, heated to 150 °C in an oil bath under high vacuum overnight and stored in the glovebox prior to use. Bromoform was purchased from Sigma Aldrich, washed with concentrated sulfuric acid until colorless, then water and $NaHCO_3$, distilled very slowly in an oil bath and kept at –20 °C in the dark for several months. Distilling bromoform with a heat gun leads to a release of bromine and affects zincocyclopropanation yield and purity. *N*-iodosuccinimide (NIS) was freshly recrystallized from dioxane/CCl_4.

7.1 Experimental Section of Chapter 2

General: During all handling, exposure of iodocyclopropanes to light should be minimized. Iodocyclopropanes may be stored for prolonged periods below 10 °C in the dark without noticeable decomposition.

7.1.1 Procedures and Characterization Data for Cyclopropanes with one Directing Group

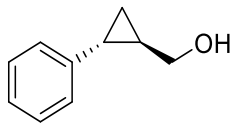
((1*R,2*R**,3*R**)-2-Iodo-3-phenylcyclopropyl)methanol (2.3) (Table 2.1, entry 2)**



In a flame-dried 50 mL round bottom flask, under argon, at −40 °C, neat diethylzinc (400 µL, 3.9 mmol, 4.4 equiv) was added to iodine (990 mg, 3.9 mmol, 4.4 equiv) and anhydrous diethyl ether (825 µL, 7.9 mmol, 8.8 equiv) in freshly distilled dichloromethane (6.0 mL). In a separate flame-dried 5 mL microwave vial, (cinnamyloxy)trimethylsilane[191] **2.1b** (184 mg, 0.9 mmol, 1.0 equiv) was weighed and purged under argon for 5 minutes, then dissolved in freshly distilled dichloromethane (4.0 mL). After 10 minutes at −40 °C, the substrate solution was transferred into the EtZnI•2Et_2O via a cannula. In another separate flame-dried 20 mL microwave vial, iodoform

(373 mg, 0.9 mmol, 2.2 equiv) was weighed and purged under argon for 5 minutes, then dissolved in freshly distilled dichloromethane (12.0 mL). This solution was transferred to the 50 mL flask via a cannula and the reaction was stirred at −40 °C during 5 hours. The reaction flask was cooled down to –78 °C. In a separate flame-dried 10 mL microwave vial, iodine (680 mg, 2.7 mmol, 3.0 equiv) was weighed and purged under argon, then dissolved in freshly distilled tetrahydrofuran (6.0 mL) and this solution was added via a cannula to the first flask. After 5 minutes, the bath was removed and the reaction mixture was allowed to warm up to room temperature and quenched with aqueous HCl 2 M. The cyclopropane was extracted from the aqueous layer by washing with diethyl ether (3×15 mL) and the combined organic layers were washed successively with saturated solution of sodium sulfite and brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography (10% diethyl ether/dichloromethane) to afford the desired iodocyclopropane **2.3** (103 mg, 42%) as a yellow oil. The characterization data were identical in all respect to those reported in the literature.[84] **Rf**: 0.63 (20% ethyl acetate/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.42-7.18 (m, 4 H, Ph), 7.09 (d, *J* = 7 Hz, 1 H, *p*-Ph), 4.09 (dd, *J* = 11.6, 4.7 Hz, 1 H, 1×C**H**$_2$OH), 3.68 (dd, *J* = 11.9, 8.5 Hz, 1 H, 1×C**H**$_2$OH), 2.93 (dd, *J* = 7.7, 4.6 Hz, 1 H, C**H**I), 2.10 (dd, *J* = 5.7, 4.9 Hz, 1 H, C**H**$_{cyclopropyl}$Ph), 1.42-1.36 (m, 1 H, C**H**$_{cyclopropyl}$CH$_2$OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 138.5 (**C**q, Ph), 128.8 (2×**C**H, Ph), 128.1 (**C**H, Ph), 126.2 (2×**C**H, Ph), 63.5 (**C**H$_2$OH), 32.3 (**C**H$_{cyclopropyl}$Ph), 26.0 (**C**H$_{cyclopropyl}$CH$_2$), –2.4 (**C**HI).

((1*R,2*R**)-2-Phenylcyclopropyl)methanol (2.5) (Table 2.1, entry 2)**



In a flame-dried 50 mL round bottom flask, under argon, at −40 °C, neat diethylzinc (400 µL, 3.9 mmol, 4.4 equiv) was added to iodine (990 mg, 3.9 mmol, 4.4 equiv) and anhydrous diethyl ether (825 µL, 7.9 mmol, 8.8 equiv) in freshly distilled dichloromethane (6.0 mL). The brown solution turned colorless. In a separate flame-dried 5 mL microwave vial, (cinnamyloxy)trimethylsilane[191] **2.1b** (184 mg, 0.9 mmol, 1.0 equiv) was weighed and purged under argon for 5 minutes, then dissolved in freshly distilled dichloromethane (4.0 mL). After 10 minutes at −40 °C, the substrate solution was transferred into the EtZnI•2Et$_2$O via a cannula. In

another separate flame-dried 20 mL microwave vial, iodoform (373 mg, 0.9 mmol, 2.2 equiv) was weighed and purged under argon for 5 minutes, then dissolved in freshly distilled dichloromethane (12.0 mL). This solution was transferred to the 50 mL flask via a cannula and the reaction was stirred at −40 °C during 5 hours. The reaction flask was cooled down to –78 °C. In a separate flame-dried 10 mL microwave vial, iodine (680 mg, 2.7 mmol, 3.0 equiv) was weighed and purged under argon, then dissolved in freshly distilled tetrahydrofuran (6.0 mL) and this solution was added via a cannula to the first flask. After 5 minutes, the bath was removed and the reaction mixture was allowed to warm up to room temperature and quenched with aqueous HCl 2 M. The cyclopropane was extracted from the aqueous layer by washing with diethyl ether (3×15 mL) and the combined organic layers were washed successively with saturated solution of sodium sulfite and brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography (10% diethyl ether/dichloromethane) to afford the desired cyclopropanes **2.5** (28 mg, 21%) as a colorless oil. The characterization data were identical in all respect to those reported in the literature.[85] **Rf**: 0.23 (20 % ethyl acetate/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.30-7.25 (m, 2 H, Ph), 7.20-7.15 (m, 1 H, Ph), 7.10-7.07 (m, 2 H, Ph), 3.67-3.59 (m, 2 H, C**H**$_2$OH), 1.86-1.82, 1 H C**H**$_{cyclopropyl}$Ph), 1.75 (br s, 1 H, O**H**), 1.51-1.43 (m, 1 H, C**H**$_{cyclopropyl}$CH$_2$OH), 1.01-0.92 (m, 2 H, C**H$_2$**$_{cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 142.8 (**C**q, Ph), 128.7 (2×**C**H, Ph), 126.2 (2×**C**H, Ph), 126.0 (**C**H, Ph), 67.0 (**C**H$_2$OH), 25.7 (**C**H$_{cyclopropyl}$Ph), 21.7 (**C**H$_{cyclopropyl}$CH$_2$OH), 14.2 (**C**H$_{2cyclopropyl}$).

7.1.2 General Procedures A-C

7.1.2.1 General Procedure A: Synthesis of Allylic Alcohols

In a flame-dried round bottom flask, under argon, at 0 °C, sodium hydride (60% dispersion in mineral oil, 1.2 equiv) was added in portions over 20 minutes to (*Z*)-but-2-ene-1,4-diol (3.0 equiv) in THF (0.70 M) to give a yellow suspension. NaH must be added very slowly to avoid di-deprotonation, which leads to di-Bn product. The ice bath was removed and the reaction was allowed to warm to room temperature and stirred 60 minutes. Then, the reaction mixture was cooled down to 0 °C again, then freshly distilled benzyl bromide derivative (1.0 equiv) was added dropwise over 10 minutes. The ice bath was removed and the reaction was allowed to warm to room temperature and stirred overnight, then poured on a saturated aqueous solution of ammonium chloride. The allylic alcohol was extracted from the aqueous layer by washing three times with

diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure to obtain a yellow liquid. The residue was purified by flash chromatography (15-40% EtOAc/hexanes) to afford benzyl protected allylic alcohols **2.6a-k**.

7.1.2.2 General Procedure B: Zincocyclopropanation with 1.5 equivalents of Carbenoid

In a flame-dried 20 mL microwave vial, under argon, neat diethylzinc (160 µL, 1.6 mmol, 2.05 equiv) was added to dried zinc iodide (500 mg, 1.6 mmol, 2.05 equiv) and anhydrous diethyl ether (660 µL, 6.3 mmol, 8.25 equiv) in freshly distilled dichloromethane (3.5 mL) at room temperature. Upon observation of full dissolution of the reaction mixture (about 1 hour), the flask was cooled down to 0 °C with a water/ice bath. Allylic alcohol (0.76 mmol, 1.00 equiv) was weighed in a separate flame-dried 5 mL microwave vial, purged under argon during 5 minutes, then dissolved in freshly distilled dichloromethane (0.5 mL). This solution was added via a cannula to the first vial. After 10 minutes at 0 °C, the reaction flask was cooled down to –78 °C in a dry ice/acetone bath and distilled bromoform (100 µL, 1.1 mmol, 1.50 equiv) was added to give a pale yellowish suspension. After 30 minutes at –78 °C, the bath was removed, the reaction mixture was stirred 3 hours at room temperature. The reaction flask was cooled down to –78 °C again. In a separate flame-dried 10 mL microwave vial, iodine (970 mg, 3.8 mmol, 5.00 equiv) was weighed and purged under argon, then dissolved in freshly distilled tetrahydrofuran (2.0 mL) and this solution was added via a cannula to the first flask. After 5 minutes, the bath was removed and the reaction mixture was allowed to warm up to room temperature and quenched with aqueous HCl 2 M. The cyclopropane was extracted from the aqueous layer by washing with diethyl ether (3×10 mL) and the combined organic layers were washed successively with saturated solution of sodium sulfite and brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate/hexanes or 20% diethyl ether/dichloromethane when the reaction was incomplete) to afford the desired cyclopropanes **2.7a-f**, **h-j**,**n**.

7.1.2.3 General Procedure C: Zincocyclopropanation with 2.0 equivalents of Carbenoid

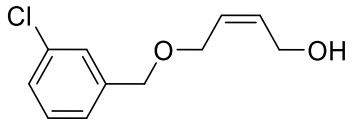
In a flame-dried 20 mL microwave vial, neat diethylzinc (203 µL, 2.0 mmol, 2.6 equiv) was added to dried zinc iodide (633 mg, 2.0 mmol, 2.6 equiv) and anhydrous diethyl ether (833 µL, 7.9 mmol, 10.4 equiv) in dichloromethane (3.5 mL) under argon at room temperature. Upon observation of

full dissolution of the reaction mixture (about 1 hour), the flask was cooled down to 0 °C with a water/ice bath. In a separate flame-dried 5 mL microwave vial, allylic alcohol (0.76 mmol, 1.0 equiv) was dissolved in dichloromethane (0.5 mL). This solution was added via a cannula to the first flask. After 10 minutes at 0 °C, the reaction flask was cooled down to –78 °C in a dry ice/acetone bath and freshly distilled bromoform (133 μL, 1.5 mmol, 2.0 equiv) was added to give a yellowish solution. After 30 minutes at that temperature, the bath was removed, the reaction mixture was allowed to warm up to room temperature and stirred 3 hours. The reaction flask was cooled down to –78 °C again. In a separate flame-dried 10 mL microwave vial, iodine (970 mg, 3.8 mmol, 5.0 equiv) was dissolved in tetrahydrofuran (2 mL) and this solution was added via a cannula to the first flask. After 5 minutes, the reaction mixture was allowed to warm up to room temperature and quenched with aqueous HCl 2 M. The cyclopropane was extracted from the aqueous layer by washing with diethyl ether (3×10 mL) and the combined organic layers were washed successively with saturated solution of sodium sulfate and brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure. The residue was purified by flash chromatography (0-30% ethyl acetate/hexanes or 0-20% diethyl ether/dichloromethane when the reaction was incomplete) to afford the desired cyclopropane **2.7g** and **2.7k**.

7.1.3 Characterization Data

7.1.3.1 Characterization Data for Allylic Alcohols

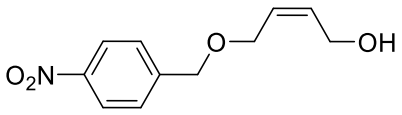
(*Z*)-4-((3-Chlorobenzyl)oxy)but-2-en-1-ol (2.6c)



Allylic alcohol **2.6c** was synthesized using general procedure A using 40 mmol of *m*-chlorobenzyl bromide as the starting material and obtained as a yellow liquid (2.07 g, 72%). **Rf**: 0.19 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.37 (s, 1 H, *o*-Ar), 7.31-7.30 (m, 2 H, Ar), 7.25-7.23 (m, 1 H, Ar), 5.89-5.85 (m, 1 H, =CH), 5.79-5.75 (m, 1 H, =CH), 4.52 (s, 2 H, OC**H$_2$**Ar), 4.22 (t, *J* = 5.7 Hz, 2 H, CHC**H$_2$**OCH$_2$Ar), 4.13 (dd, *J* = 4.2, 0.55 Hz, 2 H, CHC**H$_2$**OH), 1.72-1.68 (m, 1 H, O**H**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 140.0 (**C**q-Cl), 134.4 (**C**q, Ar), 132.5

(=**C**H), 129.8 (=**C**H), 128.2 (**C**H, Ar), 127.9 (**C**H, Ar), 127.8 (**C**H, Ar), 125.7 (**C**H, Ar), 71.6 (O**C**H_2Ar), 65.9 (**C**H_2O**C**H_2Ar), 58.8 (**C**H_2OH). **FTIR** (cm^{-1}) (neat): 3385 br (OH), 2861, 1600, 1576, 1475, 1431, 1206, 1077, 1029, 869, 782, 683, 412. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{11}H_{13}ClO_2$ $[M+Na]^+$: 235.0496; found 235.0502, 236.0531 (3:1 ratio).

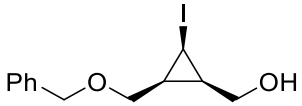
(*Z*)-4-((4-Nitrobenzyl)oxy)but-2-en-1-ol (2.6d)



Allylic alcohol **2.6d** was synthesized using general procedure A using 40 mmol of *p*-nitrobenzyl bromide as the starting material and obtained as a yellow liquid (818 mg, 27%). **Rf**: 0.16 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.23 (m, *J* = 8.7 Hz, 2 H, Ar), 7.53 (m, *J* = 8.7 Hz, 2 H, Ar), 5.91-5.87 (m, 1 H, =CH), 5.81-5.76 (m, 1 H, =CH), 4.65 (s, 2 H, OC**H**$_2$Ar), 4.25 (t, *J* = 5.9 Hz, 2 H, CHC**H**$_2$OCH_2Ar), 4.20a (d, *J* = 6.3 Hz, 2 H, CHC**H**$_2$OH), 1.61 (t, *J* = 5.7 Hz, 1 H, O**H**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 147.5 (**C**q-NO_2), 145.6 (**C**q, Ar), 132.6 (=**C**H), 127.9 (=**C**H), 127.8 (2×**C**H, Ar), 123.7 (2×**C**H, Ar), 71.1 (O**C**H_2Ar), 66.4 (**C**H_2O**C**H_2Ar), 58.8 (**C**H_2OH). **FTIR** (cm^{-1}) (neat): 3394 br (OH), 2859, 1605, 1517, 1344, 1086, 1015, 847, 738. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{11}H_{13}NO_4$ $[M+H]^+$: 246.0737; found 246.0731.

7.1.3.2 Characterization Data for *cis*-Iodocyclopropanes

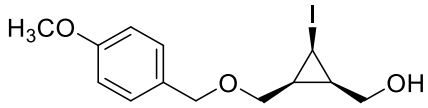
((1*R,2*S**,3*S**)-2-((benzyloxy)methyl)-3-iodocyclopropyl)methanol (2.7a)**



Iodocyclopropane **2.7a** was synthesized using general procedure B using (*Z*)-4-(benzyloxy)but-2-en-1-ol[192] **2.6a** as the starting material and obtained as a colorless oil (174.5 mg, 86% yield). **Rf**: 0.25 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.41-7.36 (m, 4 H, Ph), 7.36-7.32 (m, 1 H, *p*-Ph), 4.60 (s, 2 H, PhC**H**$_2$O), 3.90-3.82 (m, 2 H, C**H**$_2$OH), 3.62 (dd, *J* = 12.1, 8.7 Hz, 1 H, 1×C**H**$_2$OBn), 3.55 (dd, *J* = 10.4, 9.1 Hz, 1 H, 1×C**H**$_2$OBn), 2.91 (t, *J* = 7.8 Hz, 1 H, C**H**I), 2.41 (br s, 1 H, O**H**), 1.31-1.28 (m, 2 H, 2×C**H**$_{cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 137.4 (**C**q, Ar), 128.6 (2×**C**H, Ar), 128.0 (**C**H, Ar), 128.0 (2×**C**H, Ar), 73.5 (O**C**H_2Ph), 72.2 (**C**H_2OBn), 64.5 (**C**H_2OH), 20.4 (**C**H$_{cyclopropyl}$), 17.5 (**C**H$_{cyclopropyl}$), –4.2 (**C**HI). **FTIR** (cm^{-1}) (neat):

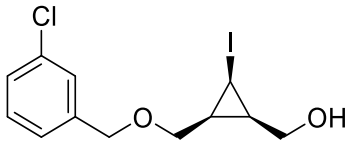
3410 br (OH), 3029, 2862, 1495, 1453, 1370, 1231, 1206, 1069, 1025, 909, 816, 736, 363, 606, 464. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{12}H_{15}IO_2$ $[M+Na]^+$: 341.0009, found 341.0012.

((1*R,2*S**,3*S**)-2-Iodo-3-(((4-methoxybenzyl)oxy)methyl)cyclopropyl)methanol (2.7b)**



Iodocyclopropane **2.7b** was synthesized using general procedure B using (*Z*)-4-((4-methoxybenzyl)oxy)but-2-en-1-ol[84] **2.6b** as the starting material and obtained as a yellowish oil (186.3 mg, 70% yield). The characterization data were identical in all respect to those reported in the literature.[84] **Rf**: 0.22 (20% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.29 (dt, *J* = 8.7, 6.6 Hz, 2 H, Ar), 6.89 (dt, *J* = 8.7, 6.6 Hz, 2 H, Ar), 4.53 (d, *J* = 14.0 Hz, 1 H, 1×OC**H**$_2$Ar), 4.50 (d, *J* = 14.0 Hz, 1 H, 1×OC**H**$_2$Ar), 3.88-3.81 (m, 5 H, OC**H**$_3$, C**H**$_2$OH, C**H**$_2$OPMB), 3.60 (ddd, *J* = 11.5, 8.4, 2.7 Hz, 1 H, 1×C**H**$_2$OPMB), 3.52 (dd, *J* = 10.3, 9.2 Hz, 1 H, 1×C**H**$_2$OH), 2.90 (t, *J* = 7.7 Hz, 1 H, C**H**I), 2.65 (dd, *J* = 9.5, 3.4 Hz, 1 H, O**H**), 1.33-1.23 (m, 2 H, 2×C**H**$_{cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 159.5 (**C**qOMe, Ar), 129.7 (2×**C**H, Ar), 129.5 (**C**q, Ar), 114.0 (2×**C**H, Ar), 73.1 (O**C**H$_2$Ar), 71.8 (**C**H$_2$OPMB), 64.5 (**C**H$_2$OH), 55.3 (O**C**H$_3$), 20.3 (**C**H$_{cyclopropyl}$), 17.5 (**C**H$_{cyclopropyl}$), –4.1 (**C**HI). **FTIR** (cm^{-1}) (neat): 3443 br (OH), 2932, 2865, 1612, 1513, 1247, 1175, 1081, 1033, 818. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{17}IO_3$ $[M+Na]^+$: 371.0115, found 371.0130.

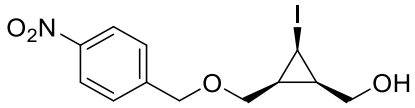
((1*R,2*S**,3*S**)-2-(((3-Chlorobenzyl)oxy)methyl)-3-iodocyclopropyl)methanol (2.7c)**



Iodocyclopropane **2.7c** was synthesized using general procedure B using (*Z*)-4-((3-chlorobenzyl)oxy)but-2-en-1-ol **2.6c** as the starting material and obtained as a yellowish oil (203.2 mg, 75% yield). **Rf**: 0.35 (40% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.38 (s, 1 H, *o*-Ar), 7.35-7.29 (m, 2 H, Ar), 7.27-7.25 (m, 1 H, Ar), 4.57 (s, 2 H, OC**H**$_2$Ar), 3.88-3.79 (m, 2 H, C**H**$_2$O), 3.65 (dd, *J* = 12.2, 8.2 Hz, 1 H, 1×C**H**$_2$OH), 3.57 (dd, *J* = 10.3, 8.6 Hz, 1 H, 1×C**H**$_2$O), 2.92 (t, *J* = 7.8 Hz, 1 H, C**H**I), 2.23 (br s, 1 H, O**H**), 1.35-1.26 (m, 2 H, 2×C**H**$_{cyclopropyl}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 139.5 (**C**qCl, Ar), 134.5 (**C**q, Ar), 129.9 (**C**H, Ar), 128.1 (**C**H, Ar), 127.9 (**C**H, Ar), 125.8 (**C**H, Ar), 72.6 (O**C**H_2Ar), 72.3 (**C**H_2O**C**H_2Ar), 64.4 (**C**H_2OH), 20.4 (**C**$H_{cyclopropyl}$), 17.6 (**C**$H_{cyclopropyl}$), –4.1 (**C**HI). **FTIR** (cm^{-1}) (neat): 3402 br (OH), 2918, 2866, 1600, 1576, 1475, 1431, 1372, 1232, 1206, 1099, 1076, 1024, 888, 780, 705, 682, 598, 432. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{12}H_{14}ClIO_2$ $[M+NH_4]^+$: 370.0065, found 370.0065.

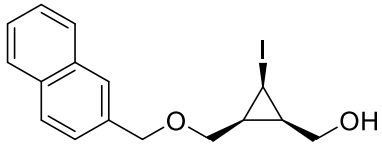
((1*R,2*S**,3*S**)-2-Iodo-3-(((4-nitrobenzyl)oxy)methyl)cyclopropyl)methanol (2.7d)**



Iodocyclopropane **2.7d** was synthesized using general procedure B using (*Z*)-4-((4-nitrobenzyl)oxy)but-2-en-1-ol **2.6d** as the starting material and obtained as a yellowish oil (183.3 mg, 58% yield). **Rf**: 0.19 (40% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.25 (dt, *J* = 8.8, 6.6 Hz, 2 H, Ar), 7.56 (dt, *J* = 8.8, 6.6 Hz, 2 H, Ar), 4.70 (s, 2 H, OC**H$_2$**Ar), 3.85 (ddd, *J* = 10.6, 8.3, 2.9 Hz, 2 H, OC**H$_2$**), 3.69-3.63 (m, 2 H, C**H$_2$**OH), 2.94 (t, *J* = 7.7 Hz, 1 H, C**H**I), 1.61 (s, 1 H, O**H**), 1.33 (tt, *J* = 7.6, 5.0 Hz, 2 H, 2×C**H**$_{cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 147.6 (**C**q-NO_2, Ar), 145.0 (**C**q, Ar), 128.0 (2×**C**H, Ar), 123.8 (2×**C**H, Ar), 72.8 (O**C**H_2Ar), 72.1 (**C**H_2O**C**H_2Ar), 64.4 (**C**H_2OH), 20.4 (**C**$H_{cyclopropyl}$), 17.7 (**C**$H_{cyclopropyl}$), –4.0 (**C**HI). **FTIR** (cm^{-1}) (neat): 3415 br (OH), 2865, 1605, 1518, 1345, 1233, 1091, 1016, 849, 739. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{12}H_{14}NIO_4$ $[M+Na]^+$: 385.9860, found 385.9850.

Note: **2.7d** could not be separated from 2 mol% of 2-(((4-nitrobenzyl)oxy)methyl)cyclopropyl) methanol **2.8d**.

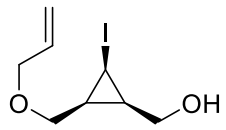
((1*R,2*S**,3*S**)-2-Iodo-3-((naphthalen-2-ylmethoxy)methyl)cyclopropyl)methanol (2.7e)**



Iodocyclopropane **2.7e** was synthesized using general procedure B using (*Z*)-4-(naphthalen-2-ylmethoxy)but-2-en-1-ol[193] **2.6e** as the starting material and obtained as yellow crystals (69.4 mg, 25% yield). **mp**.: 54-57 °C. **Rf**: 0.47 (10% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.89-7.86 (m, 3 H, Ar), 7.83 (s, 1 H, Ar), 7.54-7.49 (m, 3 H, Ar), 4.76 (s, 2 H, OC**H$_2$**Ar), 3.92-

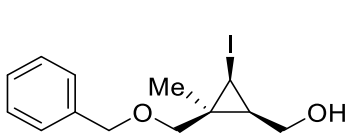
3.89 (m, 1 H, 1×C**H**$_2$OH), 3.86-3.82 (m, 2 H, 1×C**H**$_2$OH), 3.67-3.58 (m, 2 H, OC**H**$_2$CH), 2.91 (t, *J* = 7.8 Hz, 1 H, C**H**I), 2.62 (br s, 1 H, O**H**), 1.32-1.30 (m, 2 H, 2×C**H**$_{cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 134.9 (**C**q, Ar), 133.3 (**C**q, Ar), 133.1 (**C**q, Ar), 128.5 (**C**H, Ar), 127.9 (**C**H, Ar), 127.8 (**C**H, Ar), 126.9 (**C**H, Ar), 126.3 (**C**H, Ar), 126.1 (**C**H, Ar), 125.8 (**C**H, Ar), 73.6 (O**C**H$_2$-Ar), 72.2 (**C**H$_2$OCH$_2$Ar), 64.5 (**C**H$_2$OH), 20.4 (**C**H$_{cyclopropyl}$), 17.6 (**C**H$_{cyclopropyl}$), –4.1 (**C**HI). **FTIR** (cm^{-1}) (neat): 3431 br (OH), 2053, 2864, 1372, 1232, 1123, 1085, 1027, 856, 817, 752, 475. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{16}H_{17}IO_2$ $[M+K]^+$: 406.9905, found 406.9909.

((1*R,2*S**,3*S**)-2-((Allyloxy)methyl)-3-iodocyclopropyl)methanol (2.7f)**



Iodocyclopropane **2.7f** was synthesized using general procedure B using (*Z*)-4-(allyloxy)but-2-en-1-ol[194] **2.6f** as the starting material and obtained as a colorless liquid (135.1 mg, 66% yield). **Rf**: 0.20 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.94 (ddt, *J* = 17.2, 10.4, 5.8, Hz, 1 H, C**H**=CH$_2$), 5.33 (dq, *J* = 17.2, 1.4 Hz, 1 H, 1×CH=C**H**$_2$), 5.25 (dq, *J* = 10.4, 1.4 Hz, 1 H, 1×CH=C**H**$_2$), 4.09 (ddd, *J* = 12.5, 5.7, 1.3 Hz, 1 H, 1×C**H**$_2$CH=CH$_2$), 4.04 (ddd, *J* = 12.5, 5.7, 1.3 Hz, 1 H, 1×C**H**$_2$CH=CH$_2$), 3.85 (td, *J* = 10.5, 6.1 Hz, 2 H, C**H$_2$**OH), 3.61 (dd, *J* = 12.2, 8.8 Hz, 1 H, 1×CHC**H**$_2$O), 3.51 (dd, *J* = 10.4, 9.2 Hz, 1 H, 1×CHC**H**$_2$O), 2.91 (t, *J* = 7.8 Hz, 1 H, C**H**I), 2.68 (br s, 1H, O**H**), 1.34-1.23 (m, 2 H, 2×C**H**$_{cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$**)** δ ppm 133.9 (**C**H=CH$_2$), 118.0 (CH=**C**H$_2$), 72.15 (O**C**H$_2$-CH=CH$_2$), 72.08 (**C**H$_2$OH), 64.5 (**C**H$_2$O-allyl), 20.3 (**C**H$_{cyclopropyl}$), 17.4 (**C**H$_{cyclopropyl}$), –4.2 (**C**HI). **FTIR** (cm^{-1}) (neat): 3406 br (OH), 2861, 1416, 1231, 1072, 1019, 924, 594, 558. **HRMS** (ESI, Pos) *m/z*: calcd for $C_8H_{13}IO_2$ $[M+Na]^+$: 290.9852, found 290.9850.

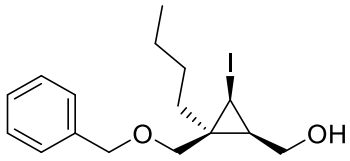
((1*R,2*S**,3*S**)-2-((Benzyloxy)methyl)-3-iodo-2-methylcyclopropyl)methanol (2.7g)**



Iodocyclopropane **2.7g** was synthesized using general procedure B using (*Z*)-4-(benzyloxy)-3-methylbut-2-en-1-ol[195] **2.6g** as the starting material and obtained as a colorless oil (210.5 mg, 83% yield). **Rf**: 0.41 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.40-7.32 (m,

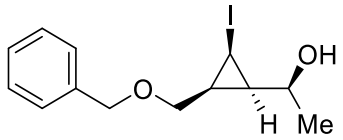
5 H, Ph), 4.63 (d, *J* = 11.8 Hz, 1 H, 1×OC**H**$_2$Ph), 4.57 (d, *J* = 11.8 Hz, 1 H, 1×OC**H**$_2$Ph), 3.83 (dd, *J* = 12.1, 6.4 Hz, 1 H, 1×C**H**$_2$OH), 3.68 (d, *J* = 10.0 Hz, 1 H, 1×C**H**$_2$OBn), 3.63 (d, *J* = 10.0 Hz, 1 H, 1×C**H**$_2$OBn), 3.54 (dd, *J* = 12.1, 9.3 Hz, 1 H, 1×C**H**$_2$OH), 2.78 (br s, 1 H, O**H**), 2.64 (d, *J* = 7.9 Hz, 1 H, C**H**I), 1.30 (s, 3 H, C**H**$_3$), 1.08 (ddd, *J* = 9.3, 7.9, 6.4 Hz, 1 H, C**H**$_{cyclopropyl}$CH$_2$OH). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 137.4 (**C**q, Ar), 128.6 (2×**C**H, Ar), 128.0 (**C**H, Ar), 127.9 (2×**C**H, Ar), 76.7 (O**C**H$_2$Ph), 73.6 (**C**H$_2$OBn), 65.3 (**C**H$_2$OH), 28.1 (**C**H$_{cyclopropyl}$), 23.6 (**C**H$_3$), 22.6 (**C**q$_{cyclopropyl}$), 2.1 (**C**HI). **FTIR** (cm^{-1}) (neat): 3419 br (OH), 3029, 2955, 925, 2901, 2861, 1454, 1414, 1361, 1226, 1087, 1071, 1027, 737, 698, 608. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{17}IO_2$ $[M+K]^+$: 370.9905, found 370.9910.

((1*R,2*S**,3*S**)-2-((Benzyloxy)methyl)-2-butyl-3-iodocyclopropyl)methanol (2.7h)**



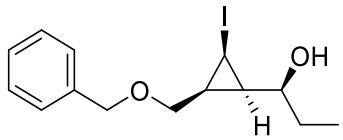
Iodocyclopropane **2.7h** was synthesized using general procedure C using (*Z*)-3-((benzyloxy)methyl)hept-2-en-1-ol[195] **2.6h** as the starting material and obtained as a yellow oil (236.9 mg, 83% yield). **Rf**: 0.28 (20% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.40-7.34 (m, 5 H, Ph), 4.62 (d, *J* = 11.7 Hz, 1 H, 1×OC**H**$_2$Ph), 4.55 (d, *J* = 11.7 Hz, 1 H, 1×OC**H**$_2$Ph), 3.83 (ddd, *J* = 12.1, 10.3, 6.4 Hz, 1 H, 1×C**H**$_2$OH), 3.78 (dd, *J* = 10.1, 0.6 Hz, 1 H, 1×C**H**$_2$OBn), 3.56 (dd, *J* = 10.1, 0.6 Hz, 1 H, 1×C**H**$_2$OBn), 3.54 (dt, *J* = 9.2, 2.7 Hz, 1 H, 1×C**H**$_2$OH), 2.84 (dq, *J* = 10.1, 2.3 1 H, O**H**), 2.66 (d, *J* = 8.0 Hz, 1 H, C**H**I), 1.85 (td, *J* = 14.9, 6.9 Hz, 1 H, 1×C**H**$_2$C$_3$H$_7$), 1.37-1.24 (m, 4 H, CH$_2$C**H**$_2$C**H**$_2$CH$_3$), 1.14 (td, *J* = 14.4, 6.9 Hz, 1 H, 1×C**H**$_2$C$_3$H$_7$), 1.06 (ddd, *J* = 9.2, 8.0, 6.4 Hz, 1 H, C**H**$_{cyclopropyl}$CH$_2$OH), 0.90 (t, *J* = 7.3 Hz, 3 H, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 137.4 (Cq, Ar), 128.6 (2×CH, Ar), 128.02 (CH, Ar), 128.97 (2×CH, Ar), 74.3 (O**C**H$_2$Ph), 73.5 (**C**H$_2$OH), 65.2 (**C**H$_2$OBn), 37.0 (**C**H$_2$CH$_2$CH$_2$CH$_3$), 28.1 (**C**H$_2$CH$_3$), 27.7 (**C**H$_{cyclopropyl}$), 26.4 (**C**q$_{cyclopropyl}$), 22.8 (**C**H$_2$CH$_3$), 14.1 (**C**H$_3$), 1.6 (**C**HI). **FTIR** (cm^{-1}) (neat): 3432 br (OH), 2954, 2927, 2857, 1454, 1364, 1223, 1069, 1027, 735, 697, 609. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{16}H_{23}IO_2$ $[M+Na]^+$: 397.0635, found 397.0649.

((1*R,2*S**,3*R**)-2-((Benzyloxy)methyl)-3-iodocyclopropyl)ethanol (2.7i)**



Iodocyclopropane **2.7i** as synthesized using general procedure C using (*Z*)-5-(benzyloxy)pent-3-en-2-ol[84] **2.6i** as the starting material and obtained as a colorless oil (185.8 mg, 73% yield). The characterization data were identical in all respect to those reported in the literature.[84] **Rf**: 0.30 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.42-7.38 (m, 4 H, Ph), 7.34-7.32 (m, 1 H, *p*-Ph), 4.60 (d, *J* = 11.8 Hz, 1 H, 1×OC**H**$_2$Ph), 4.55 (d, *J* = 11.8 Hz, 1 H, 1×OC**H**$_2$Ph), 3.69 (dqd, *J* = 9.9, 6.2, 2.6 Hz 1 H, C**H**OH), 3.58 (tt, *J* = 7.5, 6.8 Hz, 2 H, C**H**$_2$OBn), 2.91 (t, *J* = 7.5 Hz, 1 H, C**H**I), 2.05 (d, *J* = 2.6 Hz, 1 H, O**H**), 1.39 (d, *J* = 6.2 Hz, 3 H, C**H**$_3$), 1.29 (dq, *J* = 10.2, 7.5 Hz, 1 H, C**H**$_{cyclopropyl}$CH$_2$OBn), 1.02 (td, *J* = 9.9, 7.5 Hz, 1 H, C**H**$_{cyclopropyl}$CHOH). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 137.9 (**C**q, Ph), 128.5 (2×**C**H, Ph), 127.9 (2×**C**H, Ph), 127.8 (**C**H, Ph), 73.4 (O**C**H$_2$Ph), 71.1 (**C**H$_2$OBn), 69.3 (**C**HOH), 26.5 (**C**H$_3$), 22.2 (**C**H$_{cyclopropyl}$), 19.1 (**C**H$_{cyclopropyl}$), –1.7 (**C**HI). **FTIR** (cm^{-1}) (neat): 3427 br (OH), 2970, 2860, 1454, 1371, 1233, 1090, 1028, 940, 738, 698, 608. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{17}IO_2N$ $[M+Na]^+$: 355.0165, found 355.0179.

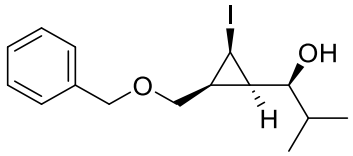
((1*R,2*S**,3*R**)-2-((Benzyloxy)methyl)-3-iodocyclopropyl)propan-1-ol (2.7j)**



Iodocyclopropane **2.7j** was synthesized using general procedure C using (*Z*)-6-(benzyloxy)hex-4-en-3-ol[84] **2.6j** as the starting material and obtained as a colorless oil (179.0 mg, 69% yield). The characterization data were identical in all respect to those reported in the literature.[84] **Rf**: 0.24 (20% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.39-7.38 (m, 4 H, Ph), 7.34-7.32 (m, 1 H, Ph), 4.61 (d, *J* = 11.7 Hz, 1 H, 1×OC**H**$_2$Ph), 4.54 (d, *J* = 11.7 Hz, 1 H, 1×OC**H**$_2$Ph), 3.63 (dd, *J* = 10.0, 6.5 Hz, 1 H, 1×C**H**$_2$OBn), 3.53 (dd, *J* = 10.0, 7.7 Hz, 1 H, 1×C**H**$_2$OBn), 3.42 (ddd, *J* = 10.0, 7.6, 4.3 Hz, 1 H, C**H**OH), 2.92 (t, *J* = 7.6 Hz, 1 H, C**H**I), 2.03 (br s, 1 H, O**H**), 1.75-1.62 (m, 2 H, C**H**$_2$CH$_3$), 1.29 (dtd, *J* = 10.0, 7.7, 6.5 Hz, 1 H, **C**H$_{cyclopropyl}$CH$_2$OBn), 1.04 (tdq, *J* = 7.6, 5.7,

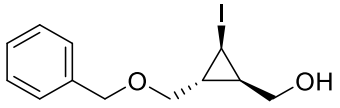
2.4 Hz, 1 H, **C**H$_{cyclopropyl}$CHOH), 1.02 (t, *J* = 7.3 Hz, 3 H, CH$_2$C**H$_3$**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.0 (**C**q, Ph), 128.5 (2×**C**H, Ph), 127.9 (2×**C**H, Ph), 127.8 (**C**H, Ph), 74.0 (**C**HOH), 73.4 (O**C**H$_2$Ph), 71.2 (**C**H$_2$OBn), 29.3 (**C**H$_2$CH$_3$), 25.2 (**C**H$_{cyclopropyl}$), 19.3 (**C**H$_{cyclopropyl}$), 10.1 (**C**H$_3$), – 1.6 (**C**HI). **FTIR** (cm^{-1}) (neat): 3445 br (OH), 2962, 2924, 1496, 1454, 1371, 1233, 1088, 968, 804, 737, 698, 606, 459. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{14}H_{19}IO_2$ $[M+Na]^+$: 369.0322, found 369.0325.

((1*R,2*S**,3*R**)-2-((Benzyloxy)methyl)-3-iodocyclopropyl)-2-methylpropan-1-ol (2.7k)**



Iodocyclopropane **2.7k** was synthesized using general procedure C using (*Z*)-6-(benzyloxy)-2-methylhex-4-en-3-ol[84] **2.6k** as the starting material and obtained as a colorless oil (187.5 mg, 68% yield). The characterization data were identical in all respect to those reported in the literature.[84] **Rf**: 0.34 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.40-7.37 (m, 4 H, Ph), 7.34-7.31 (m, 1 H, *p*-Ph), 4.61 (d, *J* = 11.7 Hz, 1 H, 1×OC**H**$_2$Ph), 4.55 (d, *J* = 11.7 Hz, 1 H, 1×OC**H**$_2$Ph), 3.69 (dd, *J* = 10.0, 5.7 Hz, 1 H, 1×C**H**$_2$OBn), 3.49 (dd, *J* = 10.0, 8.3 Hz, 1 H, 1×C**H**$_2$OBn), 3.27 (dd, *J* = 10.0, 4.7 Hz, 1 H, C**H**OH), 2.94 (t, *J* = 7.6 Hz, 1 H, C**H**I), 1.99 (br s, 1 H, O**H**), 1.84 (ttd, *J* = 6.9, 6.8, 4.7 Hz, 1 H, C**H**$(CH_3)_3$), 1.31 (dtd, *J* = 10.1, 8.3, 5.7 Hz, 1 H, C**H**$_{cyclopropyl}$CH$_2$OBn), 1.10 (td, *J* = 10.1, 7.7 Hz, 1 H, C**H**$_{cyclopropyl}$CHOH), 1.03 (d, *J* = 6.8 Hz, 3 H, C**H$_3$**), 1.01 (d, *J* = 6.8 Hz, 3 H, C**H$_3$**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.0 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.9 (2×**C**H, Ph), 127.8 (**C**H, Ph), 76.7 (**C**HOH), 73.5 (**C**H$_2$OPh), 71.3 (**C**H$_2$OBn), 33.3 (**C**H$(CH_3)_3$), 23.6 (**C**H$_{cyclopropyl}$), 20.0 (**C**H$_{cyclopropyl}$), 19.4 (**C**H$_3$), 17.2 (**C**H$_3$), –1.1 (**C**HI). **FTIR** (cm^{-1}) (neat): 3495, 2959, 2871, 1496, 1367, 1235, 1156, 1091, 1027, 988, 806, 737, 698, 611. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{15}H_{21}IO_2$ $[M+Na]^+$: 383.0478, found 383.0480.

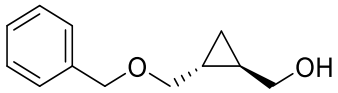
((1*R,2*R**,3*S**)-2-((Benzyloxy)methyl)-3-iodocyclopropyl)methanol (2.7n) (Scheme 2.9)**



Cyclopropane **2.7n** was synthesized using general procedure B using (*E*)-4-(benzyloxy)but-2-en-1-ol[85] **2.6n** as the starting material and obtained as a yellowish oil (48.4 mg, 20% yield). The

characterization data were identical in all respect to those reported in the literature.[85] **Rf**: 0.54 (30% ethyl acetate/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.38-7.26 (m, 5 H, Ph), 4.54 (d, *J* = 1.2 Hz, 1 H, 1×PhC**H**$_2$O), 4.49 (d, *J* = 1.1 Hz, 1 H, 1×PhC**H**$_2$O), 3.90-3.82 (m, 2 H, C**H$_2$**OH), 3.39 (dd, *J* = 11.2, 7.1 Hz, 1 H, 1×BnOC**H$_2$**), 3.27 (dd, *J* = 10, 6 Hz, 1H, 1×BnOC**H$_2$**), 2.55 (ddd, *J* = 7.5, 4.6, 1.2 Hz, 1 H, C**H**I), 2.13 (br s, 1 H, O**H**), 1.38-1.31 (m, 1 H, C**H**$_{cyclopropyl}$CH$_2$OBn), 0.98-0.91 (m, 1 H, C**H**$_{cyclopropyl}$CH$_2$OH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 138.4 (**C**q, Ph), 128.8 (2×**C**H, Ph), 128.1 (2×**C**H, Ph), 127.9 (**C**H, Ph), 73.7 (O**C**H$_2$Ph), 73.0 (**C**H$_2$OBn), 71.0 (**C**H$_2$OH), 28.6 (**C**H$_{cyclopropyl}$), 27.8 (**C**H$_{cyclopropyl}$), –6.2 (**C**HI).

((1*R,2*R**)-2-((Benzyloxy)methyl)cyclopropyl)methanol (2.8n) (Scheme 2.9)**



Cyclopropane **2.8n** was synthesized using general procedure B using (*E*)-4-(benzyloxy)but-2-en-1-ol[85] **2.6n** as the starting material and obtained as a colorless oil (59.9 mg, 41% yield). The characterization data were identical in all respect to those reported in the literature.[85] **Rf**: 0.13 (30% ethyl acetate/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.38-7.29 (m, 5 H, Ph), 4.56 (s, 2 H, PhC**H$_2$**O), 3.64-3.53 (m, 4 H, BnOC**H$_2$**CH$_{cyclopropyl}$, HOC**H$_2$**CH$_{cyclopropyl}$), 1.87 (br. s, 1 H, O**H**), 1.09-1.00 (m, 2 H, C**H**$_{cyclopropyl}$CHOH, C**H**$_{cyclopropyl}$CHOBn), 0.54-0.49 (m, 2 H, C**H$_2$**$_{cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 138.8 (**C**q, Ar), 128.8 (2×**C**H, Ar), 128.1 (2×**C**H, Ar), 128.0 (**C**H, Ar), 73.8 (O**C**H$_2$Ph), 73.0 (**C**H$_2$OBn), 66.7 (**C**H$_2$OH), 20.2 (**C**H$_{cyclopropyl}$), 17.2 (**C**H$_{cyclopropyl}$), 8.5 (**C**H$_{2cyclopropyl}$).

7.1.4 Procedures and Characterization Data for Deprotected Iodocyclopropane 2.9

((1*R,2*S**,3*R**)-3-Iodocyclopropane-1,2-diyl)dimethanol (2.9)**

In a 10 mL round bottom flask, cerium chloride heptahydrate (161 mg, 0.43 mmol, 1.5 equiv) was added to iodocyclopropane **2.7b** (104 mg, 0.30 mmol, 1.0 equiv) in MeCN (2.0 mL, 0.15 M). Sodium iodide, (45 mg, 0.30 mmol, 1.0 equiv) was successively added to give an orange

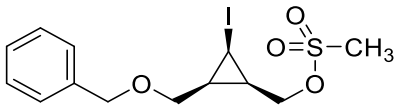
suspension. The reaction mixture was heated to reflux in an oil bath during 24 h, then allowed to cool down to room temperature. Sodium sulfate was added, the mixture was filtered, and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (2% MeOH in CH_2Cl_2) to afford cyclopropane **2.9** (51.0 mg, 75 %) as a yellow oil. **Rf**: 0.26 (2% MeOH/CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 4.04-3.96 (m, 2 H, 1×C**H$_2$**OH), 3.75-3.65 (m, 2 H, 1×C**H$_2$**OH), 2.90 (t, *J* = 7.7 Hz, 1 H, C**H**I), 2.26 (br s, 2 H, 2×O**H**), 1.33-1.24 (m, 2 H, 2×C**H**$_{cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 64.6 (2×**C**H_2OH), 20.4 (2×**C**$H_{cyclopropyl}$), 19.8 (**C**$H_{cyclopropyl}$), –4.5 (**C**HI). **FTIR** (cm^{-1}) (neat): 3319 br (OH), 2931, 2882, 1410, 1230, 1021, 810, 646, 604, 564. **HRMS** (ESI, Neg) *m/z*: calcd for $C_5H_9IO_2$ $[M–H]^-$: 226.9575, found 226.9583.

7.2 Experimental Section of Chapter 3

General: During all handling, exposure of iodocyclopropanes and iodocyclobutanes to light should be minimized.

7.2.1 Procedures and Characterization Data for Cyclopropanes 3.20 and 3.21

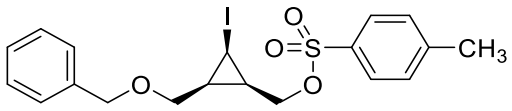
((1*R,2*S**,3*R**)-2-((Benzyloxy)methyl)-3-iodocyclopropyl)methyl methanesulfonate (3.20)**



In a flame-dried 5 mL microwave vial, triethylamine (0.07 mL, 0.52 mmol, 1.1 equiv) was added to iodocyclopropylmethanol **2.7a** (150 mg, 0.47 mmol 1.0 equiv) in dichloromethane (1.5 mL, 0.30 M) at 0 °C in an ice bath. Then, methanesulfonyl chloride (0.04 mL, 0.52 mmol, 1.1 equiv), was added. The reaction mixture was allowed to warm up to room temperature, stirred during 30 minutes, then quenched with a saturated solution of sodium bicarbonate. The cyclopropane was extracted from the aqueous layer by washing with dichloromethane (3×5 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered into a 50 mL round bottom flask. The volatiles were removed under reduced pressure to afford cyclopropane **3.20** (186 mg, 99%) as a yellow oil. **Rf**: 0.55 (50% ethyl acetate/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.83 (d, *J* = 4.5 Hz, 4 H, Ph), 7.36-3.31 (m, 1 H, *p*-Ph, Ph), 4.59 (d, *J* = 16.2 Hz, 1 H, 1×OC**H$_2$**Ph), 4.55 (d, *J* = 16.3 Hz, 1 H, 1×OC**H$_2$**Ph), 4.48-4.44 (m, 1 H, 1×C**H$_2$**O), 4.26-4.21 (m, 1 H, 1×C**H$_2$**O), 3.68-3.63 (m, 1 H, 1×C**H$_2$**O), 3.59-3.55 (m, 1 H, 1×C**H$_2$**O), 3.05 (s,

3 H, C**H**$_3$), 3.0 (t, *J* = 7.7 Hz, C**H**I), 1.44-1.38 (m, 2 H, 2×C**H**$_{cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 137.8 (**C**q), 128.0 (2×**C**H), 127.5 (2×**C**H), 127.9 (**C**H), 73.3 (O**C**H_2Ph), 72.6 (**C**H_2OBn), 68.5 (**C**H_2OMs), 18.5 (**C**H$_{cyclopropyl}$), 15.3 (**C**H$_{cyclopropyl}$), −3.6 (**C**HI). **FTIR** (cm^{-1}) (neat): 2845, 3062, 3016, 1576, 1474, 1367, 1189, 1173, 1095, 944, 812, 653, 544, 515. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{17}IO_4S$ $[M+NH_4]^+$: 414.0230, found 414.0232.

((1*R,2*S**,3*R**)-2-((Benzyloxy)methyl)-3-iodocyclopropyl)methyl 4-methylbenzenesulfonate (3.21)**



In a flame-dried 5 mL microwave vial, triethylamine (0.07 mL, 0.52 mmol, 1.1 equiv) was added to iodocyclopropylmethanol **2.7a** (150 mg, 0.47 mmol 1.0 equiv) in dichloromethane (1.5 mL, 0.30 M) at 0 °C in an ice bath. Then, *p*-toluenesulfonyl chloride (98.9 mg, 0.52 mmol, 1.1 equiv), then 4-dimethylaminopyridine (3.6 mg, 0.03 mmol, 5 mol%) were added. The reaction mixture was allowed to warm up to room temperature, stirred during 12 h, then quenched with a saturated solution of sodium bicarbonate. The cyclopropane was extracted from the aqueous layer by washing with dichloromethane (3×5 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered into a 50 mL round bottom flask. The volatiles were removed under reduced pressure to afford cyclopropane **3.21** (220 mg, 99%) as a yellow oil. **Rf**: 0.63 (50% ethyl acetate/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.83 (d, *J* = 8.3 Hz, 2 H, Ar), 7.45-3.35 (m, 8 H, Ph, Ar), 4.53 (d, *J* = 17.6 Hz, 1 H, 1×OC**H**$_2$Ph), 4.50 (d, *J* = 17.6 Hz, 1 H, 1×OC**H**$_2$Ph), 4.27-4.22 (m, 1 H, 1×C**H**$_2$O), 4.10-4.05 (m, 1 H, 1×C**H**$_2$O), 3.05-3.46 (m, 2 H, C**H**$_2$O), 2.91 (t, *J* = 7.6 Hz, C**H**I), 2.48 (s, 3 H, C**H**$_3$), 1.33-1.27 (m, 2 H, 2×C**H**$_{cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 144.8 (**C**q-Me, Ar), 137.8 (**C**q), 133.0 (**C**q), 129.9 (2×**C**H), 128.5 (2×**C**H), 128.1 (2×**C**H, Ar), 127.9 (2×**C**H), 127.8 (**C**H), 73.3 (O**C**H_2Ph), 72.2 (**C**H_2OBn), 70.7 (**C**H_2OTs), 21.7 (**C**H_3), 18.8 (**C**H$_{cyclopropyl}$), 17.2 (**C**H$_{cyclopropyl}$), −3.6 (**C**HI). **FTIR** (cm^{-1}) (neat): 2866, 3063, 3006, 1596, 1454, 1364, 1188, 1174, 1096, 947, 814, 655, 554, 529. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{19}H_{21}IO_4S$ $[M+NH_4]^+$: 490.0543, found 490.0552.

7.2.2 General Procedures D-F and Scale-Up Procedure

7.2.2.1 General Procedure D: Cyclization of Iodocyclopropylmethanols

In a flame-dried 20 mL microwave vial, triethylamine (1.1 equiv) was added to iodocyclopropylmethanol **2.7a-k** (1.0 equiv) in dichloromethane (0.30 M) at 0 °C in an ice bath. Then, methanesulfonyl chloride (1.1 equiv) was added. The reaction mixture was allowed to warm up to room temperature, stirred during 30 minutes, then quenched with a saturated solution of sodium bicarbonate. The cyclopropane was extracted from the aqueous layer by washing with dichloromethane (3×5 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered into a 50 mL round bottom flask. The volatiles were removed under reduced pressure. A septum and a magnetic stir bar were added and the flask was purged with argon during 5 minutes. Freshly distilled tetrahydrofuran (0.05 M) was added and the reaction flask was cooled down to –78 °C in a dry ice/acetone bath. Freshly titrated *n*-butyllithium (2.5 M in THF, 2.2 equiv) was added over 15 minutes using a syringe pump (2 mL/h). The reaction flask was stirred at –78 °C during 45 minutes, then the dry ice/acetone bath was removed and the flask was allowed to warm up to room temperature and stirred another 45 minutes. The reaction mixture was quenched with a saturated solution of sodium bicarbonate, the bicyclo[1.1.0]butane was extracted from the aqueous layer by washing with diethyl ether (3×10 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were carefully removed under reduced pressure to obtain bicyclo[1.1.0]butanes **3.22a-k**. The residue was used as is for next step.

7.2.2.2 Scale-up Procedure for Cyclization of Iodocyclopropylmethanol

In a flame-dried 100 mL round-bottom flask, triethylamine (1.6 mL, 11.4 mmol, 1.1 equiv) was added to iodocyclopropylmethanol **2.7a** (3.3 g, 10.3 mmol, 1.0 equiv) in dichloromethane (35 mL, 0.30 M) at 0 °C in an ice bath. Then, methanesulfonyl chloride (0.9 mL, 11.4 mmol, 1.1 equiv) was added dropwise. The reaction mixture was allowed to warm up to room temperature, stirred during 30 minutes, then quenched with a saturated solution of sodium bicarbonate. The cyclopropane was extracted from the aqueous layer by washing with dichloromethane (3×20 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered into a 500 mL round bottom flask. The volatiles were removed under reduced pressure. A septum and a magnetic stir bar were added and the flask was purged with argon during 5 minutes. Freshly

distilled tetrahydrofuran (200 mL, 0.05 M) was added and the reaction flask was cooled down to – 78 °C in a dry ice/acetone bath. *n*-Butyllithium (10.3 mL, 2.5 M in THF, 22.8 mmol, 2.2 equiv) was added over 120 minutes using a syringe pump (5 mL/h, syringe pump addition). The reaction flask was stirred at –78 °C during 45 minutes, then the ice/acetone bath was removed and the flask was allowed to warm up to room temperature and stirred another 45 minutes. The reaction mixture was quenched with a saturated solution of sodium bicarbonate, the bicyclo[1.1.0]butane was extracted from the aqueous layer by washing with diethyl ether (3×50 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were carefully removed under reduced pressure to obtain bicyclo[1.1.0]butane **3.22a** (1.55-1.64 g, 8.9-9.1 mmol, 89-91%). The residue was used as is for the next step.

7.2.2.3 General Procedure E: Ring Opening of Bicyclo[1.1.0]butanes

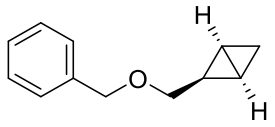
In a flame-dried 5 mL microwave vial, pyridinium *p*-toluenesulfonate (0.25 equiv) was added to bicyclo[1.1.0]butanes **3.22a-k** (1.00 equiv) in methanol (0.40 M) at 0 °C in an ice bath. The reaction mixture was allowed to warm up to room temperature and stirred during 30 minutes. The reaction mixture was quenched with an aqueous saturated solution of sodium bicarbonate, the desired compound was extracted from the aqueous layer by washing with dichloromethane (3×5 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (0-20% diethyl ether/hexanes) to afford the ring-opened compounds **3.23a-h** and **3.27g-k**.

7.2.2.4 General Procedure F: Ring Opening of Bicyclo[1.1.0]butanes using various alcohols

In a flame-dried 5 mL microwave vial, pyridinium *p*-toluenesulfonate (25.0 mg, 0.1 mmol, 0.25 equiv) was added to bicyclo[1.1.0]butane **3.22a** (69.7 mg, 0.4 mmol, 1.00 equiv) in the corresponding alcohol (0.40 M) at 0 °C in an ice bath. The reaction mixture was allowed to warm up to room temperature and stirred during 30 minutes. The reaction mixture was quenched with an aqueous saturated solution of sodium bicarbonate, the desired compound was extracted from the aqueous layer by washing with dichloromethane (3×5 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (2% diethyl ether/hexanes) to afford the ring-opened compounds **3.23l-o**.

7.2.3 Characterization Data for BCBs and Corresponding Ring-Opened Adducts

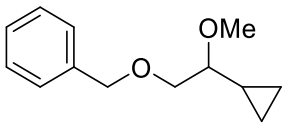
(1*R,3*S**)-2-((Benzyloxy)methyl)bicyclo[1.1.0]butane (3.22a)**



Bicyclo[1.1.0]butane **3.22a** was synthesized using general procedure D, using iodocyclopropane **2.7a** (1.40 g, 4.4 mmol) as the starting material and obtained as a colorless liquid (700.8 mg, 91% yield). The crude was purified by a rapid flash column chromatography (2% diethyl ether/pentane) on silica gel to afford a colorless liquid (291.1 mg, 38% yield). **Rf**: 0.49 (10% diethyl ether/pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.37-7.36 (m, 4 H, Ph), 7.31-7.30 (m, 1 H, *p*-Ph), 4.57 (s, 2 H, OC**H$_2$**Ph), 3.29 (d, *J* = 6.9 Hz, 2 H, C_{BCB}HC**H$_2$**OBn), 2.64 (tt, *J* = 6.9, 3.4 Hz, 1 H, C_{BCB}**H**CH_2O), 1.83 (td, *J* = 3.1, 1.7 Hz, 1 H, 1×C_{BCB}**H$_2$**), 1.57 (td, *J* = 3.6, 1.5 Hz, 2 H, 2×C_{BCB}**H**), 1.41 (d, *J* = 1.7 Hz, 1 H, 1×C_{BCB}**H$_2$**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.6 (**C**q, Ph), 128.3 (2×**C**H, Ph), 127.7 (2×**C**H, Ph), 127.5 (**C**H, Ph), 72.6 (O**C**H_2Ph), 63.7 (**C**H_2OBn), 45.8 ($\mathbf{C}_{BCB}HCH_2OBn$), 30.2 ($\mathbf{C}_{BCB}H_2$), 1.2 (2×$\mathbf{C}_{BCB}$H). **FTIR** (cm^{-1}) (neat): 3029, 2985, 2904, 2855, 1496, 1454, 1345, 1143, 1075, 1028, 989, 721, 697, 608. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{12}H_{14}O$ $[M+H]^+$: 175.1117, found 175.1117.

Note: Product is very acid sensitive, volatile and has a short half-life at room temperature. It can be kept at –20 °C under argon for 2-3 days. It decomposes over silica.

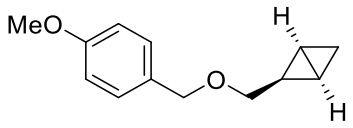
((2-Cyclopropyl-2-methoxyethoxy)methyl)benzene (3.23a)



Cyclopropane **3.23a** was synthesized using general procedure E using crude BCB **3.22a** (139.4 mg, 0.8 mmol) as the starting material. The crude was purified by flash column chromatography on silica gel to afford a colorless liquid (99.3 mg, 54% yield). **Rf**: 0.11 (5% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.38-7.35 (m, 4 H, Ph), 7.32-7.30 (m, 1 H, *p*-Ph), 4.63 (d, *J* = 12.2 Hz, 1 H, 1×OC**H$_2$**Ph), 4.60 (d, *J* = 12.2 Hz, 1 H, 1×OC**H$_2$**Ph), 3.65 (dd, *J* = 10.3, 3.3 Hz, 1 H,

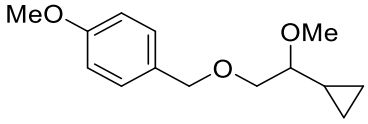
1×C**H**$_2$OBn), 3.59 (dd, *J* = 10.3, 6.3 Hz, 1 H, 1×C**H**$_2$OBn), 3.50 (s, 3 H, OC**H**$_3$), 2.74 (ddd, *J* = 8.6, 6.5, 3.3 Hz, 1 H, C**H**OMe), 0.87 (dtt, *J* = 8.6, 5.0, 2.5 Hz, 1 H, C**H**$_{cyclopropyl}$), 0.70-0.63 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.51-0.40 (m, 2 H, 2×C**H**$_{2cyclopropyl}$), 0.17-0.10 (m, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.5 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.6 (2×**C**H, Ph), 127.5 (**C**H, Ph), 84.5 (**C**HOMe), 73.4 (O**C**H$_2$Ph), 73.1 (**C**H$_2$OBn), 57.4 (O**C**H$_3$), 11.8 (**C**H$_{cyclopropyl}$), 4.4 (**C**H$_{2cyclopropyl}$), 0.6 (**C**H$_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3065, 3029, 3005, 2978, 2926, 2893, 2856, 2824, 1454, 1364, 1199, 1097, 1027, 822, 736, 698 **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{18}O_2$ $[M+Na]^+$: 229.1199, found 229.1203.

(1*R,3*S**)-2-(((4-Methoxybenzyl)oxy)methyl)bicyclo[1.1.0]butane (3.22b)**



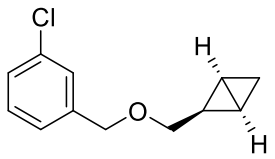
Bicyclo[1.1.0]butane **3.22b** was synthesized using general procedure D, using iodocyclopropane **2.7b** (97.5 mg, 0.3 mmol) as the starting material and obtained as a colorless liquid (89% yield). The crude was purified by flash column chromatography (2% diethyl ether/pentane) on silica gel to afford a colorless liquid (13.7 mg, 24% yield). **Rf**: 0.44 (5% diethyl ether/pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.29 (dt, *J* = 8.4, 6.6 Hz, 2 H, Ar), 6.89 (dt, *J* = 8.6, 6.6 Hz, 2 H, Ar), 4.49 (s, 2 H, OC**H**$_2$Ar), 3.83 (s, 3 H, OC**H**$_3$), 3.26 (d, *J* = 6.9 Hz, 2 H, C$_{BCB}$HC**H**$_2$OPMB), 2.63 (tt, *J* = 6.9, 3.4 Hz, 1 H, C$_{BCB}$**H**CH$_2$O), 1.82 (td, *J* = 3.1, 1.7 Hz, 1 H, 1×C$_{BCB}$**H**$_2$), 1.56 (td, *J* = 3.2, 1.5 Hz, 2 H, 2×C$_{BCB}$**H**), 1.40 (q, *J* = 1.4 Hz, 1 H, 1×C$_{BCB}$**H**$_2$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 159.1 (**C**q-OMe, Ar), 130.7 (**C**q, Ar), 129.3 (2×**C**H, Ar), 113.7 (2×**C**H, Ar), 72.2 (O**C**H$_2$Ar), 63.4 (**C**H$_2$OPMB), 45.8 (O**C**H$_3$), 55.3 (**C**$_{BCB}$HCH$_2$O), 30.2 (**C**$_{BCB}$H$_2$), 1.2 (2×**C**$_{BCB}$H). **FTIR** (cm^{-1}) (neat): 2986, 2934, 2906, 2836, 1612, 1512, 1301, 1245, 1173, 1143, 1079, 1035, 819, 721. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{16}O_2$ $[M+H]^+$: 205.1223, found 205.1225.

1-((2-Cyclopropyl-2-methoxyethoxy)methyl)-4-methoxybenzene (3.23b)



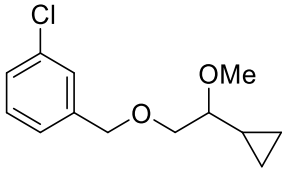
Cyclopropane **3.23b** was synthesized using general procedure E using crude BCB **3.22b** (51.1 mg, 0.2 mmol) as the starting material. The crude was purified by flash column chromatography on silica gel to afford a colorless liquid (27.2 mg, 46% yield). **Rf**: 0.23 (10% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.30 (dt, *J* = 8.8, 6.6 Hz, 2 H, Ar), 6.90 (dt, *J* = 8.4, 6.6 Hz, 2 H, Ar), 4.56 (d, *J* = 11.9 Hz, 1 H, 1×OC**H**$_2$Ph), 4.52 (d, *J* = 11.9 Hz, 1 H, 1×OC**H**$_2$Ph), 3.83 (s, 3 H, OC**H**$_3$), 3.61 (dd, *J* = 10.3, 3.3 Hz, 1 H, 1×C**H**$_2$OBn), 3.55 (dd, *J* = 10.3, 6.6 Hz, 1 H, 1×C**H**$_2$OBn), 3.49 (s, 3 H, OC**H**$_3$), 2.72 (ddd, *J* = 8.7, 6.6, 3.3 Hz, 1 H, C**H**OMe), 0.90-0.81 (m, 1 H, C**H**$_{cyclopropyl}$), 0.68-0.62 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.49-0.39 (m, 2 H, 2×C**H**$_{2cyclopropyl}$), 0.16-0.09 (m, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 159.1 (**C**q, Ar), 130.5 (**C**q, Ar), 129.2 (2×**C**H, Ar), 113.7 (2×**C**H, Ar), 84.5 (**C**HOMe), 73.0 (O**C**H$_2$Ph), 72.8 (**C**H$_2$OBn), 57.3 (O**C**H$_3$), 55.3 (O**C**H$_3$), 11.8 (**C**H$_{cyclopropyl}$), 4.4 (**C**H$_{2cyclopropyl}$), 0.6 (**C**H$_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3003, 2931, 2896, 2858, 2836, 1613, 1513, 1464, 1363, 1301, 1247, 1173, 1095, 1035, 821. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{14}H_{20}O_3$ $[M+Na]^+$: 259.1305, found 259.1301.

(1*R,3*S**)-2-(((3-Chlorobenzyl)oxy)methyl)bicyclo[1.1.0]butane (3.22c)**



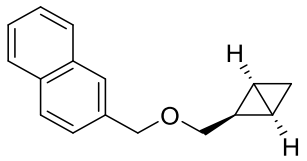
Bicyclo[1.1.0]butane **3.22c** was synthesized using general procedure D using iodocyclopropane **2.7c** (211.6 mg, 0.6 mmol) as the starting material, obtained as a colorless liquid (95% yield) and used as is for next step. Yield was determined by ^{1}H-NMR analysis of the crude mixture. Due to instability, only ^{1}H NMR could be obtained. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.37 (s, 1 H, Ar), 7.27-7.24 (m, 3 H, Ar), 4.53 (s, 2 H, OC**H**$_2$Ar), 3.29 (d, *J* = 7.0 Hz, 2 H, C_{BCB}HC**H**$_2$OCH$_2$Ar), 2.64 (tt, *J* = 6.9, 3.4 Hz, 1 H, C_{BCB}**H**CH$_2$O), 1.84 (td, *J* = 3.2, 1.8 Hz, 1 H, 1×C_{BCB}**H**$_2$), 1.58 (td, *J* = 3.3, 1.3 Hz, 2 H, 2×C_{BCB}**H**), 1.41-1.40 (m, 1 H, 1×C_{BCB}**H**$_2$).

1-Chloro-3-((2-cyclopropyl-2-methoxyethoxy)methyl)benzene (3.23c)



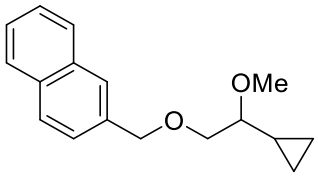
Cyclopropane **3.23c** was synthesized using general procedure E using BCB **3.22c** (0.6 mmol) as the starting material. The crude was purified by flash column chromatography on silica gel to afford colorless liquid (74.3 mg, 46% yield). **Rf**: 0.21 (5% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.39 (s, 1 H, Ar), 7.32-7.23 (m, 3 H, Ar), 4.58 (s, 2 H, OC**H**$_2$Ph), 3.65 (dd, *J* = 10.3, 3.2 Hz, 1 H, 1×C**H**$_2$OBn), 3.59 (dd, *J* = 10.3, 6.4 Hz, 1 H, 1×C**H**$_2$OBn), 3.50 (s, 3 H, OC**H**$_3$), 2.74 (dd, *J* = 8.7, 6.4, 3.2Hz, 1 H, C**H**OMe), 0.92-0.83 (m, 1 H, C**H**$_{cyclopropyl}$), 0.71-0.65 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.53-0.47 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.47-0.41 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.18-0.10 (m, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 140.6 (**C**q, Ar), 134.3 (Cq, Ar), 129.6 (**C**H, Ar), 127.6 (**C**H, Ar), 127.6 (**C**H, Ar), 125.5 (**C**H, Ar), 84.5 (**C**HOMe), 73.3 (O**C**H$_2$Ph), 72.6 (**C**H$_2$OBn), 57.4 (O**C**H$_3$), 11.7 (**C**H$_{cyclopropyl}$), 4.5 (**C**H$_{2cyclopropyl}$), 0.6 (**C**H$_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3004, 2927, 2894, 2859, 2824, 1600, 1576, 1431, 1359, 1198, 1097, 1022, 948, 868, 779, 682. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{17}ClO_2$ $[M+Na]^+$: 263.0809, found 263.0810.

2-((((1*R,3*S**)-Bicyclo[1.1.0]butan-2-yl)methoxy)methyl)naphthalene (3.22e)**



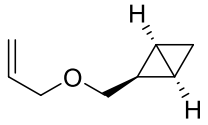
Bicyclo[1.1.0]butane **3.22e** was synthesized using general procedure D using iodocyclopropane **2.7e** (220.9 mg, 0.6 mmol) as the starting material, obtained as a colorless liquid (53% yield) and used as is for next step. Yield was determined by ^{1}H-NMR analysis of the crude mixture using triphenylmethane as the internal standard. Due to instability, only ^{1}H NMR could be obtained. **Rf**: 0.51 (10% diethyl ether/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.86-7.83 (m, 2 H, Ar), 7.81 (s, 1 H, Ar), 7.51-7.48 (m, 2 H, Ar), 7.25-7.23 (m, 1 H, Ar), 7.15-7.13 (m, 1 H, Ar), 4.73 (s, 2 H, OC**H**$_2$Ar), 3.33 (d, *J* = 7.1 Hz, 2 H, C$_{BCB}$HC**H**$_2$O), 2.64 (tt, *J* = 7.1, 3.3 Hz, 1 H, C$_{BCB}$**H**CH$_2$O), 1.84-1.82 (m, 1 H, 1×C$_{BCB}$**H**$_2$), 1.59-1.56 (m, 2 H, 2×C$_{BCB}$**H**), 1.41 (d, *J* = 1.4, 1 H, 1×C$_{BCB}$**H**$_2$).

2-((2-Cyclopropyl-2-methoxyethoxy)methyl)naphthalene (3.23e)



Cyclopropane **3.23e** was synthesized using general procedure E using BCB **3.22e** (80.7 mg, 0.4 mmol) as the starting material. The crude was purified by flash column chromatography on silica gel to afford colorless liquid (81.5 mg, 53% yield). **Rf**: 0.30 (10% diethyl ether /hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.89-7.84 (m, 3 H, Ar), 7.83 (s, 1 H, Ar), 7.57-7.46 (m, 3 H, Ar), 4.80 (d, *J* = 12.5 Hz, 1 H, 1×OC**H**$_2$Ph), 4.77 (d, *J* = 12.5 Hz, 1 H, 1×OC**H**$_2$Ph), 3.69 (dd, *J* = 10.3, 3.3 Hz, 1 H, 1×C**H**$_2$OBn), 3.64 (dd, *J* = 10.3, 6.5 Hz, 1 H, 1×C**H**$_2$OBn), 3.52 (s, 3 H, OC**H**$_3$), 2.77 (ddd, *J* = 8.7, 6.5, 3.3 Hz, 1 H, C**H**OMe), 0.94-0.85 (m, 1 H, C**H**$_{cyclopropyl}$), 0.71-0.64 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.51-0.40 (m, 2 H, 2×C**H**$_{2cyclopropyl}$), 0.17-0.10 (m, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 136.0 (**C**q, Ar), 133.3 (**C**q, Ar), 133.0 (**C**q, Ar), 128.1 (**C**H, Ar), 127.9 (**C**H, Ar), 127.7 (**C**H, Ar), 126.3 (**C**H, Ar), 126.0 (**C**H, Ar), 125.8 (**C**H, Ar), 125.7 (**C**H, Ar), 84.6 (**C**HOMe), 73.5 (O**C**H_2Ph), 73.1 (**C**H_2OBn), 57.3 (O**C**H_3), 11.8 (**C**$H_{cyclopropyl}$), 4.4 (**C**$H_{2cyclopropyl}$), 0.7 (**C**$H_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3057, 3005, 2926, 2894, 2857, 2825, 1463, 1368, 1342, 1170, 1123, 1095, 1020, 949, 855, 817, 750, 475. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{17}H_{20}O_2$ $[M+NH_4]^+$: 274.1802, found 274.1810.

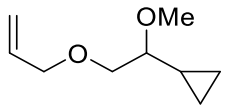
(1*R,3*S**)-2-((Allyloxy)methyl)bicyclo[1.1.0]butane (3.22f)**



Bicyclo[1.1.0]butane **3.22f** was synthesized using modified general procedure D, using iodoyclopropane **2.7f** (171.6 mg, 0.6 mmol) as the starting material and diethyl ether as the solvent. The desired compound was obtained as an orange liquid (85% yield) and used as is for next step. Yield was determined by ^{1}H-NMR analysis of the crude mixture. Due to instability, only ^{1}H NMR could be obtained. **Rf**: 0.57 (30% ethyl acetate/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 5.99-5.89 (m, 1 H, *J* = 17.3, 10.6, 5.8 Hz, CH_2=C**H**), 5.28 (ddt, *J* = 17.3, 2.6, 1.7 Hz, 1 H, 1×=C**H**$_{2(trans)}$), 5.19 (ddt, *J* = 10.6, 2.6, 1.4 Hz, 1 H, 1×=C**H**$_{2(cis)}$), 4.02 (dt, *J* = 5.8, 2.3 Hz, 2 H, OC**H**$_2$CH=CH_2),

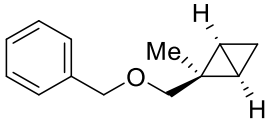
3.25 (d, J = 7.0 Hz, 2 H, $C_{BCB}HC\mathbf{H_2}O$-allyl), 2.62 (tt, J = 6.9, 3.2 Hz, 1 H, $C_{BCB}\mathbf{H}CH_2O$), 1.84-1.83 (m, 1 H, 1×$C_{BCB}\mathbf{H_2}$), 1.59-1.56 (m, 2 H, 2×$C_{BCB}\mathbf{H}$), 1.41 (d, J = 1.4, 1 H, 1×$C_{BCB}\mathbf{H_2}$).

(2-(Allyloxy)-1-methoxyethyl)cyclopropane (3.23f)



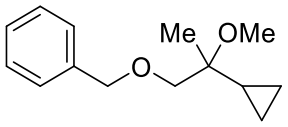
Cyclopropane **3.23f** was synthesized using general procedure E and using BCB **3.22f** (67.6 mg, 0.5 mmol) as the starting material. The crude was purified by flash column chromatography on silica gel to afford a colorless liquid (58.7 mg, 47% yield). **Rf**: 0.34 (10% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 6.00-5.90 (m, 1 H, C**H**=CH_2), 5.31 (dq, J = 17.2, 1.6 Hz, 1 H, 1×CH=C$\mathbf{H}_{2(trans)}$), 5.21 (dq, J = 10.4, 1.4 Hz, 1 H, 1×CH=C$\mathbf{H}_{2(cis)}$), 4.08-4.05 (m, 2 H, O$\mathbf{CH_2}$CH=CH_2), 3.61 (dd, J = 10.3, 3.2 Hz, 1 H, 1×O$\mathbf{CH_2}$CHOMe), 3.56 (dd, J = 10.3, 6.7 Hz, 1 H, 1×O$\mathbf{CH_2}$CHOMe), 3.50 (s, 3 H, O$\mathbf{CH_3}$), 2.72 (ddd, J = 8.8, 6.7, 3.2 Hz, 1 H, C**H**OMe), 0.89-0.81 (m, 1 H, C$\mathbf{H}_{cyclopropyl}$), 0.71-0.63 (m, 1 H, 1×C$\mathbf{H}_{2cyclopropyl}$), 0.53-0.47 (m, 1 H, 1×C$\mathbf{H}_{2cyclopropyl}$), 0.47-0.41 (m, 1 H, 1×C$\mathbf{H}_{2cyclopropyl}$), 0.19-0.12 (m, 1 H, 1×C$\mathbf{H}_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 134.9 (**C**H=CH_2), 117.0 (CH=**C**H_2), 84.5 (O**C**H_2), 73.1 (O**C**H_2CH=CH_2), 72.4 (**C**HOMe), 57.3 (O**C**H_3), 11.7 (**C**$H_{cyclopropyl}$), 4.4 (**C**$H_{2cyclopropyl}$), 0.5 (**C**$H_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3006, 2979, 2892, 2856, 1464, 1094, 1021, 995, 922, 179.10474 822, 5. **HRMS** (ESI, Pos) *m/z*: calcd for $C_9H_{16}O_2$ $[M+Na]^+$: 179.1043, found 179.1047.

(1*R,2*S**,3*S**)-2-((Benzyloxy)methyl)-2-methylbicyclo[1.1.0]butane (3.22g)**



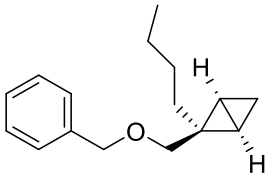
Bicyclo[1.1.0]butane **3.22g** was synthesized using general procedure D using iodocyclopropane **2.7g** (149.5 mg, 0.4 mmol) as the starting material, obtained as a colorless liquid (86% yield) and used as is for next step. Yield was determined by ^{1}H-NMR analysis of the crude mixture. Due to instability, only ^{1}H NMR could be obtained. **Rf**: 0.66 (10% diethyl ether/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 5.36-5.23 (m, 5 H, Ar), 4.57 (s, 2 H, O$\mathbf{CH_2}$Ph), 3.27 (s, 2 H, $C_{BCB}C\mathbf{H_2}$OBn), 1.79-1.77 (m, 1 H, 1×$C_{BCB}\mathbf{H_2}$), 1.36-1.34 (m, 1 H, $C_{BCB}\mathbf{H}$), 1.30-1.27 (m, 2 H, 1×$C_{BCB}\mathbf{H_2}$ and $C_{BCB}\mathbf{H}$), 1.25 (s, 3 H, C$\mathbf{H_3}$).

((2-Cyclopropyl-2-methoxypropoxy)methyl)benzene (3.23g)



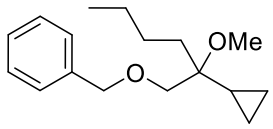
Cyclopropane **3.23g** was synthesized using general procedure E using BCB **3.22g** (72.9 mg, 0.4 mmol) as the starting material. The crude was purified by flash column chromatography on silica gel to afford colorless liquid (74.8 mg, 87% yield). **Rf**: 0.41 (10% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.41-7.34 (m, 4 H, Ph), 7.32-7.29 (m, 1 H, Ph), 4.62 (s, 2 H, OC**H$_2$**Ph), 3.46 (d, *J* = 9.8 Hz, 1 H, 1×C**H$_2$**OBn), 3.39 (d, *J* = 9.8 Hz, 1 H, 1×C**H$_2$**OBn), 3.35 (s, 3 H, OC**H$_3$**), 1.06-0.98 (m, 1 H, C**H**$_{cyclopropyl}$), 0.96 (s, 3 H, C**H$_3$**), 0.55-0.46 (m, 2 H, 2×C**H**$_{2cyclopropyl}$), 0.44-0.37 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.24-0.17 (m, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.6 (**C**q, Ph), 128.3 (2×**C**H, Ph), 127.5 (2×**C**H, Ph), 127.4 (**C**H, Ph), 76.3 (**C**qOMe), 76.0 (**C**H_2OPh), 73.4 (**C**H_2OBn), 50.2 (O**C**H_3), 16.0 (**C**H_3), 15.8 (**C**H$_{cyclopropyl}$), 1.0 (**C**$H_{2cyclopropyl}$), 0.7 (**C**$H_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 2976, 2937, 2895, 2856, 1202, 1497, 1454, 1365, 1095, 1021, 735, 697. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{14}H_{20}O_2$ $[M+Na]^+$: 243.1355, found 243.1354.

(1*R,2*S**,3*S**)-2-((Benzyloxy)methyl)-2-butylbicyclo[1.1.0]butane (3.22h)**



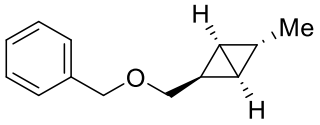
Bicyclo[1.1.0]butane **3.22h** was synthesized using general procedure D using iodocyclopropane **2.7h** (224.6 mg, 0.6 mmol) as the starting material, obtained as a colorless liquid (91% yield) and used as is for next step. Due to instability, only ^{1}H NMR could be obtained. **Rf**: 0.67 (10% diethyl ether/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 5.37-5.29 (m, 5 H, Ar), 4.56 (s, 2 H, OC**H$_2$**Ph), 3.27 (s, 2 H, C**H$_2$**OBn), 1.79-1.78 (m, 1 H, 1×C$_{BCB}$**H$_2$**), 1.56-1.53 (m, 2 H, C**H$_2$**$_{Bu}$), 1.36-1.34 (m, 4 H, 1×C$_{BCB}$**H$_2$**, C$_{BCB}$**H**, C**H$_2$**$_{Bu}$), 1.28-1.34 (m, 3 H, C**H$_2$**$_{Bu}$ and C$_{BCB}$**H**), 0.90 (t, *J* = 7.0 Hz, 3 H, C**H$_3$**).

(((2-Cyclopropyl-2-methoxyhexyl)oxy)methyl)benzene (3.23h)



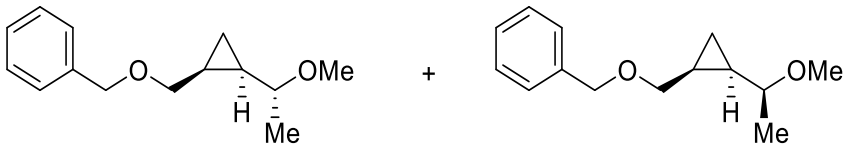
Cyclopropane **3.23h** was synthesized using general procedure E using crude BCB **3.22h** (0.6 mmol) as the starting material. The crude was purified by flash column chromatography on silica gel to afford a colorless liquid (92.5 mg, 64% yield). **Rf**: 0.41 (10% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.40-7.34 (m, 4 H, Ph), 7.33-7.29 (m, 1 H, Ph), 4.57 (d, *J* = 12.4 Hz, 1 H, 1×OC**H**$_2$Ph), 4.54 (d, *J* = 12.4 Hz, 1 H, 1×OC**H**$_2$Ph), 3.39 (d, *J* = 9.7 Hz, 1 H, 1×C**H**$_2$OBn), 3.34 (d, *J* = 9.7 Hz, 1 H, 1×C**H**$_2$OBn), 3.31 (s, 3 H, OC**H**$_3$), 1.61-1.44 (m, 2 H, C**H**$_{2Bu}$), 1.40-1.25 (m, 4 H, C**H**$_{2Bu}$, 2×C**H**$_{2cyclopropyl}$), 0.96-0.89 (m, 4 H, C**H**$_{2Bu}$, 2×C**H**$_{2cyclopropyl}$), 0.49-0.37 (m, 4 H, 1×C**H**$_{2cyclopropyl}$, C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.6 (**C**q, Ph), 128.3 (2×**C**H, Ph), 127.5 (2×**C**H, Ph), 127.4 (**C**H, Ph), 76.6 (**C**qOMe), 73.8 (O**C**H$_2$Ph), 73.4 (**C**H$_2$OBn), 50.0 (O**C**H$_3$), 31.8 (**C**H$_{2Bu}$), 25.2 (**C**H$_{2Bu}$), 23.4 (**C**H$_{2Bu}$), 16.2 (**C**H$_{2cyclopropyl}$), 14.2 (**C**H$_{cyclopropyl}$), 0.7 (**C**H$_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3008, 2954, 2934, 2860, 1455, 1362, 1206, 1097, 1026, 1097, 1026, 734, 697. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{17}H_{26}O_2$ $[M+Na]^+$: 285.1825, found 285.1831.

(1*R,2*S**,3*S**,4*S**)-2-((Benzyloxy)methyl)-4-methylbicyclo[1.1.0]butane (3.22i)**



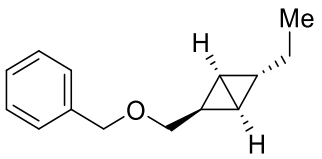
Bicyclo[1.1.0]butane **3.22i** was synthesized using general procedure D using iodocyclopropane **2.7i** (199.3 mg, 0.6 mmol) as the starting material, obtained as a colorless liquid used as is for next step. 45% Yield was determined by ^{1}H-NMR analysis of the crude mixture using triphenylmethane as the internal standard. Due to unstability, only ^{1}H NMR could be obtained. **Rf**: 0.49 (10% diethyl ether /hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.30-7.23 (m, 5 H, Ph), 4.56 (s, 2 H, OC**H**$_2$Ph), 3.29 (d, *J* = 6.9 Hz, 2 H, C_{BCB}HC**H**$_2$OBn), 2.64 (tt, *J* = 7.1, 3.6 Hz, 1 H, C_{BCB}**H**CH$_2$OBn), 1.84-1.81 (m, 1 H, C_{BCB}**H**CH$_3$), 1.37-1.36 (m, 2 H, 2×C_{BCB}**H**), 1.07 (d, *J* = 5.6 Hz, 3 H, C**H**$_3$).

((((1*S,2*R**)-2-(1-Methoxyethyl)cyclopropyl)methoxy)methyl)benzene (3.27i)**



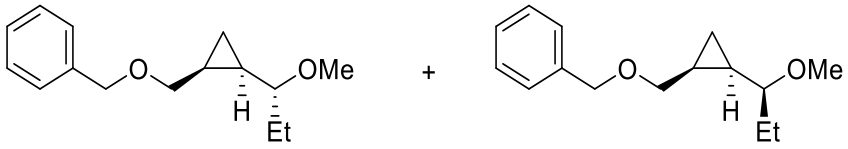
Cyclopropane **3.27i** was synthesized using general procedure E using BCB **3.22i** (0.3 mmol) as the starting material. Diastereomeric ratio (1.7:1) was determined by ^{1}H-NMR analysis of the crude mixture. The crude was purified by flash column chromatography on silica gel to afford colorless oil (62.0 mg, 99% yield). **Rf**: 0.25 (10% diethyl ether/hexanes). *Major diastereomer*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.40-7.34 (m, 4 H, Ph), 7.34-7.29 (m, 1 H, Ph), 4.58 (d, *J* = 11.9 Hz, 1 H, 1×OC**H**$_2$Ph), 4.50 (d, *J* = 11.9 Hz, 1 H, 1×OC**H**$_2$Ph), 3.65 (dd, *J* = 10.2, 6.5 Hz, 1 H, 1×C**H**$_2$OBn), 3.51-3.44 (m, 1 H, C**H**OMe), 3.41 (dd, *J* = 10.2, 8.4 Hz, 1 H, 1×C**H**$_2$OBn), 3.38 (s, 3 H, OC**H**$_3$), 1.37 (d, *J* = 6.2 Hz, 3 H, C**H**$_3$), 1.35-1.25 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 1.07 (qd, *J* = 8.6, 5.8 Hz, 1 H, C**H**$_{cyclopropyl}$), 0.84 (td, *J* = 8.6, 4.8 Hz, 1 H, C**H**$_{cyclopropyl}$), 0.35 (dd, *J* = 5.6, 4.8 Hz, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.3 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.8 (2×**C**H, Ph), 127.6 (**C**H, Ph), 77.4 (**C**HOMe), 72.8 (O**C**H$_2$Ph), 70.4 (**C**H$_2$OBn), 56.1 (O**C**H$_3$), 21.5 (**C**H$_{cyclopropy}$), 20.8 (**C**H$_3$), 13.9 (**C**H$_{cyclopropyl}$), 9.5 (**C**H$_{2cyclopropy}$). **FTIR** (cm^{-1}) (neat): 2971, 2929, 2859, 2817, 1454, 1372, 1202, 1175, 1091, 1028, 1002, 736, 698. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{14}H_{20}O_2$ $[M+H]^+$: 221.1536, found 221.1526. *Minor diastereomer*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.40-7.34 (m, 4 H, Ph), 7.34-7.29 (m, 1 H, Ph), 4.58 (s, 2 H, OC**H**$_2$Ph), 3.77 (dd, *J* = 10.3, 6.2 Hz, 1 H, 1×C**H**$_2$OBn), 3.40 (m, 1 H, 1×C**H**$_2$OBn), 3.31 (s, 3 H, C**H**$_3$), 2.95 (dt, *J* = 9.0, 6.0, Hz, 1 H, C**H**OMe), 1.28 (d, *J* = 6.0 Hz, 3 H, C**H**$_3$), 1.35-1.25 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 1.03 (qd, *J* = 8.7, 5.4 Hz, 1 H, C**H**$_{cyclopropyl}$), 0.85 (td, *J* = 8.7, 4.9 Hz, 1 H, C**H**$_{cyclopropyl}$), 0.14 (dd, *J* = 5.4, 4.9 Hz, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.6 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.7 (2×**C**H, Ph), 127.5 (**C**H, Ph), 76.6 (**C**HOMe), 72.7 (O**C**H$_2$Ph), 70.3 (**C**H$_2$OBn), 55.6 (O**C**H$_3$), 22.1 (**C**H$_{cyclopropyl}$), 19.8 (**C**H$_3$), 16.3 (**C**H$_{cyclopropyl}$), 7.7 (**C**H$_{2cyclopropyl}$).

(1*R,2*S**,3*S**,4*S**)-2-((Benzyloxy)methyl)-4-ethylbicyclo[1.1.0]butane (3.22j)**



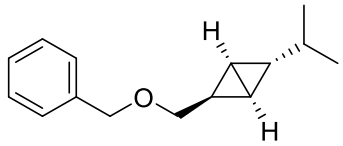
Bicyclo[1.1.0]butane **3.22j** was synthesized using general procedure D using iodocyclopropane **2.7j** (198.4 mg, 0.6 mmol) as the starting material, obtained as a colorless liquid and used as is for next step. 48% Yield was determined by ^{1}H-NMR analysis of the crude mixture using triphenylmethane as the internal standard. Due to instability, only ^{1}H NMR could be obtained. **Rf**: 0.51 (10% diethyl ether /hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.30-7.25 (m, 5 H, Ph), 4.56 (s, 2 H, OC**H$_2$**Ph), 3.29 (d, *J* = 7.1 Hz, 2 H, C_{BCB}HC**H$_2$**OBn), 2.54 (tt, *J* = 7.2, 3.4 Hz, 1 H, C_{BCB}**H**CH_2O), 1.84-1.81 (m, 1 H, C_{BCB}**H**Et), 1.40-1.36 (m, 2 H, 2×C_{BCB}**H**), 1.08-1.01 (m, 2 H, C**H$_2$**CH_3), 0.97 (t, *J* = 7.4 Hz, 3 H, C**H$_3$**).

((((1*S,2*R**)-2-(1-Methoxypropyl)cyclopropyl)methoxy)methyl)benzene (3.27j)**



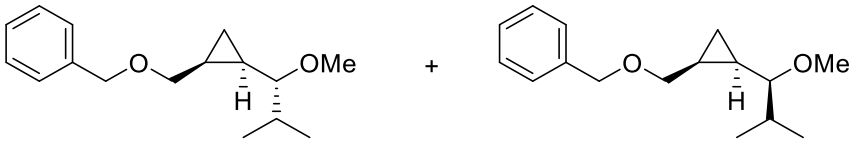
Cyclopropane **3.27j** was synthesized using general procedure E using compound **2.7j** (0.6 mmol) as the starting material. Diastereomeric ratio (1.8:1) was determined by ^{1}H-NMR analysis of the crude mixture using triphenylmethane as internal standard. The crude was purified by flash column chromatography on silica gel to afford colorless oil (55.1 mg, 81% yield). **Rf**: 0.26 (10% diethyl ether /hexanes). *Major diastereomer*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.43-7.34 (m, 4 H, Ph), 7.34-7.29 (m, 1 H, Ph), 4.58 (d, *J* = 11.8 Hz, 1 H, 1×OC**H$_2$**Ph), 4.51 (d, *J* = 11.8 Hz, 1 H, 1×OC**H$_2$**Ph), 3.50 (dd, *J* = 10.1, 7.0 Hz, 1 H, 1×C**H$_2$**OBn), 3.45 (dd, *J* = 10.1, 7.6 Hz, 1 H, 1×C**H$_2$**OBn), 3.39 (s, 3 H, C**H$_3$**), 2.83-2.76 (m, 1 H, C**H**OMe), 1.68-1.58 (m, 2 H, C**H$_2$**CH_3), 1.35-1.25 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 1.25-1.17 (m, 1 H, C**H**$_{cyclopropyl}$), 1.00-0.94 (m, 4 H, C**H**$_{cyclopropyl,}$ C**H$_3$**), 0.50-0.42 (m, 1 H, 1×C**H**$_{2cyclopropy}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.4 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.8 (2×**C**H, Ph), 127.6 (**C**H, Ph), 81.9 (**C**HOMe), 72.9 (O**C**H_2Ph), 70.4 (**C**H_2OBn), 56.3 (O**C**H_3), 27.8 (**C**H_2CH_3), 19.3 (**C**H_3), 13.9 (**C**H$_{cyclopropyl}$), 9.5 (**C**H$_{cyclopropyl}$), 9.4 (**C**$H_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 2964, 2928, 2874, 2857, 2857, 2818, 1454, 1375, 1198, 1166, 1077, 1028, 926, 735, 697, 609. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{15}H_{22}O_2$ $[M+Na]^+$: 257.1512, found 257.1510.

((1*R,2*S**,3*S**,4*S**)-2-((Benzyloxy)methyl)-4-isopropylbicyclo[1.1.0]butane (3.22k)**



Bicyclo[1.1.0]butane **3.22k** was synthesized using general procedure D using iodocyclopropane **2.7k** (216.1 mg, 0.6 mmol) as the starting material, obtained as a crude mixture and used as is for next step. 29% Yield was determined by ^{1}H-NMR analysis of the crude mixture using triphenylmethane as the internal standard. Due to instability, only ^{1}H NMR could be obtained. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.31-7.24 (m, 5 H, Ph), 4.57 (s, 2 H, 1×OC**H**$_2$Ph), 3.30 (d, *J* = 7.1 Hz, 2 H, C**H**$_2$OBn), 2.53 (tt, *J* = 7.1, 3.7 Hz, 1 H, **C**$_{BCB}$HCH$_2$O), 1.86-1.83 (m, 1 H, C$_{BCB}$**H**CH(CH$_3$)$_2$), 1.41-1.39 (m, 2 H, 2×C$_{BCB}$**H**), 0.98 (d, *J* = 6.7 Hz, 6 H, 2×C**H**$_3$), 0.85 (td, *J* = 8.4, 4.7 Hz, 1 H, C**H**(CH$_3$)$_2$).

((((1*S,2*R**)-2-(1-Methoxy-2-methylpropyl)cyclopropyl)methoxy)methyl)benzene (3.27k)**

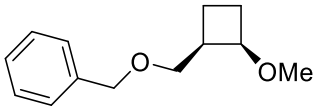


Cyclopropane **3.27k** was synthesized using general procedure E using BCB **3.22k** (0.2 mmol) as the starting material. Diastereomeric ratio (2.1:1) was determined by ^{1}H-NMR analysis of the crude mixture using triphenylmethane as internal standard. The crude was purified by flash column chromatography on silica gel to afford colorless oil (41.4 mg, 97% yield). **Rf**: 0.24 (10% diethyl ether/hexanes). *Major diastereomer*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.42-7.34 (m, 4 H, Ph), 7.34-7.29 (m, 1 H, *p*-Ph), 4.58 (d, *J* = 11.9 Hz, 1 H, 1×OC**H**$_2$Ph), 4.52 (d, *J* = 11.9 Hz, 1 H, 1×OC**H**$_2$Ph), 3.54 (dd, *J* = 10.0, 7.0 Hz, 1 H, 1×C**H**$_2$OBn), 3.42 (dd, *J* = 10.0, 7.5 Hz, 1 H, 1×C**H**$_2$OBn), 3.38 (s, 3 H, OC**H**$_3$), 2.70 (dd, *J* = 8.6, 4.2 Hz, 1 H, C**H**OMe), 1.96-1.87 (m, 1 H, C**H**(CH$_3$)$_2$), 1.24-1.14 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 1.00-0.94 (m, 8 H, 2×C**H**$_{cyclopropyl}$, 2×C**H**$_3$), 0.48 (ddd, *J* = 9.9, 5.4, 1.1 Hz, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.4 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.8 (2×**C**H, Ph), 127.6 (**C**H, Ph), 85.0 (**C**HOMe), 72.9 (O**C**H$_2$Ph), 70.6 (**C**H$_2$OBn), 57.1 (O**C**H$_3$), 32.4 (**C**H(CH$_3$)$_3$), 19.1 (**C**H$_3$), 17.6 (**C**H$_3$), 17.0 (**C**H$_{cyclopropyl}$), 14.2 (**C**H$_{yclopropyl}$), 9.0 (**C**H$_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 2959, 2872, 2818, 1454, 1365, 1197, 1167,

1089, 1028, 967, 735, 697, 609. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{16}H_{24}O_2$ $[M+Na]^+$: 271.1668, found 271.1673.

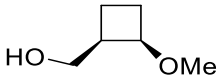
7.2.4 Procedures and Characterization Data of Post-Functionalized Adducts

((((1*R,2*R**)-2-Methoxycyclobutyl)methoxy)methyl)benzene (3.24a)**



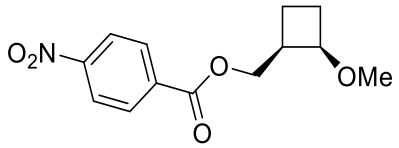
At room temperature in a 5 mL microwave vial, mercury (II) acetate (95.6 mg, 0.3 mmol, 1.0 equiv) was added to bicyclo[1.1.0]butane **3.22a** (52.3 mg, 0.3 mmol, 1.0 equiv) in MeOH (0.5 mL, 0.6 M) to give a yellow suspension. After 30 minutes, TLC showed complete conversion of starting material. Aqueous NaOH 3 M (1.50 mL, 4.5 mmol, 15.0 equiv) was added dropwise to give a grey suspension. The mixture was stirred during 10 minutes. A solution of sodium borohydride (11.9 mg, 0.3 mmol, 1.05 equiv) in NaOH 3 M (1.5 mL, 4.5 mmol, 15.0 equiv) was added dropwise using a syringe. The mixture was stirred during 30 minutes, then filtered over cotton and rinsed with diethyl ether to remove Hg(s). The cyclobutane was extracted from the aqueous layer by washing with diethyl ether (3×10 mL) and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (0-10% EtOAc /hexanes) to afford **3.24a** (32.2 mg, 52%) as a colorless liquid. **Rf**: 0.31 (10% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.40-7.34 (m, 4 H, Ph), 7.31 (dd, *J* = 5.8, 2.9 Hz, 1 H, Ph), 4.59 (d, *J* = 12.0 Hz, 1 H, OC**H**$_2$Ph), 4.54 (d, *J* = 12.0 Hz, 1 H, OC**H**$_2$Ph), 3.98 (dd, *J* = 7.4, 7.2 Hz, 1 H, C**H**OMe), 3.81 (dd, *J* = 9.4, 7.2 Hz, 1 H, C**H**$_2$OBn), 3.61 (dd, *J* = 9.4, 3.3 Hz, 1 H, C**H**$_2$OBn), 3.28 (s, 3 H, OCH_3), 2.83 (ddd, *J* = 11.0, 7.2, 3.3 Hz, 1 H, C**H**$_{cyclobutyl}$), 2.27-2.20 (m, 1 H, C**H**$_{2cyclobutyl}$), 2.08-1.98 (m, 1 H, C**H**$_{2cyclobutyl}$), 1.81-1.72 (m, 1 H, C**H**$_{2cyclobutyl}$), 1.65-1.57 (m, 1 H, C**H**$_{2cyclobutyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.7 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.7 (2×**C**H, Ph), 127.5 (**C**H, Ph), 75.2 (**C**H$_{cyclobutyl}$OMe), 73.2 (O**C**H$_2$Ph), 69.5 (**C**H$_2$OBn), 56.4 (O**C**H$_3$), 40.3 (**C**H$_{cyclobutyl}$CH$_2$OBn), 27.9 (**C**H$_{2cyclobutyl}$), 17.0 (**C**H$_{2cyclobutyl}$). **FTIR** (cm^{-1}) (neat): 2933, 2862, 1496, 1453, 1362, 1228, 1199, 1125, 1092, 1026, 844, 734, 697, 608, 557, 456. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{18}O_2$ $[M+Na]^+$: 229.1199, found 229.1191.

((1*R,2*R**)-2-Methoxycyclobutyl)methanol (3.25)**



At room temperature, in a flame-dried 25 mL round bottom flask, under nitrogen, palladium hydroxide (27.2 mg, 0.2 mmol, 20 wt. % Pd on carbon, wet) was added to methoxycyclobutane **3.23a** (200 mg, 1.0 mmol, 1.0 equiv) in freshly distilled MeOH (19.0 mL, 0.05 M). A hydrogen balloon was added and H_2 was degassed in the solution for 2 minutes, then the exit was removed and the balloon was left during the reaction. The mixture was stirred at room temperature during 15 hours, then filtered over a 1:1 ratio of celite/silica and rinsed with diethyl ether. The volatiles were carefully removed under reduced pressure (careful volatile product). The residue was purified by flash chromatography (30% diethyl ether/petroleum ether) to afford **3.25** (106 mg, 72 %) as a colorless liquid. **Rf**: 0.17 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 4.07 (ddd, $J_1 = J_2 = J_3 = 7.3$ Hz, 1 H, C**H**OMe), 3.97 (dd, $J = 11.3, 8.9$ Hz, 1 H, C**H**$_2$OH), 3.73 (dd, $J = 11.3, 5.0$ Hz, 1 H, C**H**$_2$OH), 3.27 (s, 3 H, OCH_3), 2.75 (td, $J = 7.8, 3.4$ Hz, 1 H, C**H**CH_2O), 2.52 (br s, 1 H, O**H**), 2.31-2.20 (m, 1 H, 1×C**H**$_{2\text{cyclobutyl}}$COMe), 2.13-2.00 (m, 1 H, 1×C**H**$_{2\text{cyclobutyl}}$COMe), 1.73 (dq, $J = 11.6, 8.8$ Hz, 1 H, 1×C**H**$_{2\text{cyclobutyl}}$), 1.53 (ddt, $J = 11.6, 10.8, 3.3$ Hz, 1 H, 1×C**H**$_{2\text{cyclobutyl}}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 76.1 (**C**$HOCH_3$), 63.4 (**C**H_2OH), 55.7 (O**C**H_3), 41.4 (**C**$H_{\text{cyclobutyl}}$), 27.6 (**C**$H_{2\text{cyclobutyl}}CHOCH_3$), 15.3 (**C**$H_{2\text{cyclobutyl}}$). **FTIR** ($cm^{-1}$) (neat): 3407, 2937, 2874, 2826, 1454, 1358, 1194, 1120, 1015, 883, 834, 759, 561. **HRMS** (ESI, Pos) *m/z*: calcd for $C_6H_{12}O_2$ $[M+Na]^+$: 139.0729, found 139.0727.

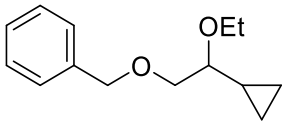
((1*R,2*R**)-2-Methoxycyclobutyl)methyl 4-nitrobenzoate (3.26)**



Under nitrogen, in a flame-dried 5 mL microwave vial, freshly distilled triethylamine (83.7 uL, 0.6 mmol, 1.5 equiv), then DMAP (catalytic amount) were added to cyclobutylmethanol **3.25** (46.5 mg, 0.4 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL, 0.80 M). The reaction mixture was cooled down to 0 °C in an ice bath, 4-nitrobenzoyl chloride (111 mg, 0.6 mmol, 1.5 equiv) in CH_2Cl_2 (0.2 mL) was added with a syringe and the reaction was stirred at room temperature during 30 minutes. The

reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and the cyclobutane was extracted from the aqueous layer by washing with diethyl ether (3×5 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (10% diethyl ether /hexanes) to afford methoxycyclobutane **3.26** (65.8 mg, 62%) as a yellow solid. **mp**: 37-39 °C. **Rf**: 0.13 (10% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.31 (dt, J = 8.9, 6.8 Hz, 2 H, Ar), 8.23 (dt, J = 8.9, 6.8 Hz, 2 H, Ar), 4.68 (dd, J = 11.3, 7.2 Hz, 1 H, C**H**$_2$O), 4.55 (dd, J = 11.3, 7.8 Hz, 1 H, C**H**$_2$O), 4.05 (ddd, $J_1 = J_2 = J_3$ = 7.3 Hz, 1 H, C**H**OMe), 3.29 (s, 3 H, OC**H**$_3$), 2.99 (dt, J = 7.3, 3.9 Hz, 1 H, C**H**CH$_2$O), 2.36-2.27 (m, 1 H, C**H**$_{2cyclobutyl}$CO), 2.21-2.11 (m, 1 H, C**H**$_{2cyclobutyl}$CO), 1.86 (tdt, J = 11.7, 9.0, 8.5, Hz, 1 H, C**H**$_{2cyclobutyl}$), 1.71 (ttd, J = 11.3, 3.5, 0.1 Hz, 1 H, C**H**$_{2cyclobutyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 164.9 (Ar**C**OO), 150.5 (**C**q-NO_2, Ar), 135.9 (**C**q, Ar), 130.7 (2×**C**H, Ar), 123.5 (2×**C**H, Ar), 74.8 (**C**HOMe), 65.2 (**C**H$_2$OCO), 56.4 (O**C**H$_3$), 39.1 (**C**HCH$_2$O), 27.9 (**C**H$_{2cyclobutyl}$CO), 16.6 (**C**H$_{2cyclobutyl}$). **FTIR** (cm^{-1}) (neat): 2933, 1722 (C=O), 1607, 1527, 1457, 1348, 1270, 1199, 1118, 1102, 1040, 1014, 957, 873, 852, 784. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{15}NO_5$ $[M+H]^+$: 266.1023, found 266.1021.

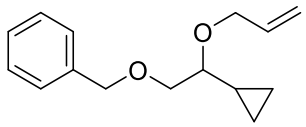
((2-Cyclopropyl-2-ethoxyethoxy)methyl)benzene (3.23l)



Cyclopropane **3.23l** was synthesized using general procedure F and anhydrous ethanol as the alcohol. The crude was purified by a flash column chromatography (5% diethyl ether/hexanes) on silica gel to afford a colorless liquid (31.7 mg, 36% yield). **Rf**: 0.14 (10% diethyl ether/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.38-7.37 (m, 4 H, Ph), 7.32-7.30 (m, 1 H, *p*-Ph), 4.63 (d, J = 12.3 Hz, 1 H, 1×OC**H**$_2$Ph), 4.59 (d, J = 12.3 Hz, 1 H, 1×OC**H**$_2$Ph), 3.80-3.73 (m, 1 H, 1×OC**H**$_2$CH$_3$), 3.67-3.57 (m, 3 H, C**H**$_2$OBn, 1× OC**H**$_2$CH$_3$), 2.87 (ddd, J = 8.5, 6.3, 3.8 Hz, 1 H, C**H**OEt), 1.25 (t, J = 7.0 Hz, 3 H, C**H**$_3$), 0.90 (dtt, J = 8.2, 5.2, 1.8 Hz, 1 H, C**H**$_{cyclopropyl}$), 0.65-0.59 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.52-0.45 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.44-0.37 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.21-0.15 (m, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 138.6 (**C**q, Ph), 128.3 (2×**C**H, Ph), 127.54 (2×**C**H, Ph), 127.46 (**C**H, Ph), 82.7 (**C**HOEt), 73.5 (O**C**H$_2$Ph), 73.3 (**C**H$_2$OBn), 65.0 (O**C**H$_2$CH$_3$), 15.7 (OCH$_2$**C**H$_3$), 12.5 (**C**H$_{cyclopropyl}$), 3.9 (**C**H$_{2cyclopropyl}$), 1.1

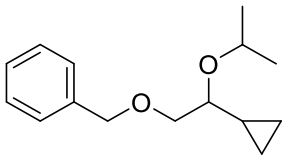
(**C**$H_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3065, 2974, 2928, 2858, 1454, 1365, 1099, 1027, 821, 735, 697. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{14}H_{20}O_2$ $[M+H]^+$: 221.1536, found 221.1537.

((2-(Allyloxy)-2-cyclopropylethoxy)methyl)benzene (3.23m)



Cyclopropane **3.23m** was synthesized using general procedure F and allylic alcohol as the alcohol. The crude was purified by a flash column chromatography (2% diethyl ether/hexanes) on silica gel to afford a colorless liquid (27.5 mg, 30% yield). **Rf**: 0.28 (10% diethyl ether/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.38-7.36 (m, 4 H, Ph), 7.36-7.30 (m, 1 H, *p*-Ph), 5.97 (ddt, *J* = 17.4, 10.4, 5.7 Hz, 1 H, C**H**=CH_2), 5.30 (dq, *J* = 17.2, 1.8 Hz, 1 H, 1×CH=C**H**$_2$), 5.18 (ddt, *J* = 10.4, 5.9, 1.3 Hz, 1 H, 1×CH=C**H**$_2$), 4.64 (d, *J* = 13.6 Hz, 2 H, 1×OC**H**$_2$Ph), 4.62 (d, *J* = 13.6 Hz, 2 H, 1×OC**H**$_2$Ph), 4.24 (qt, *J* = 5.6, 1.4 Hz, 1 H, 1×OC**H**$_2$CH=), 4.16 (qt, *J* = 5.6, 1.5 Hz, 1 H, 1×OC**H**$_2$CH=), 3.67 (dd, *J* = 10.3, 3.8 Hz, 1 H, 1×C**H**$_2$OBn), 3.63 (dd, *J* = 10.6, 6.2 Hz, 1 H, 1×C**H**$_2$OBn), 2.94 (ddd, *J* = 8.5, 6.1, 3.9 Hz, 1 H, CO**H**), 0.96-0.87 (m, 1 H, C**H**$_{cyclopropyl}$), 0.67-0.60 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.53-0.46 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.44-0.38 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.19 (sexd, *J* = 4.9, 0.8 Hz, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 138.6 (**C**q, Ph), 128.3 (2×**C**H, Ph), 127.54 (2×**C**H, Ph), 127.47 (**C**H, Ph), 116.5 (=**C**H_2), 82.1 (**C**HO), 73.6 (O**C**H_2Ph), 73.4 (**C**H_2OBn), 70.5 (**C**H_2CH=), 12.3 (**C**H$_{cyclopropyl}$), 4.1 (**C**$H_{2cyclopropyl}$), 1.1 (**C**$H_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3080, 3029, 3006, 2894, 2859, 1454, 1363, 1092, 1026, 922, 736, 698. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{15}H_{20}O_2$ $[M+H]^+$: 250.1802, found 250.1793.

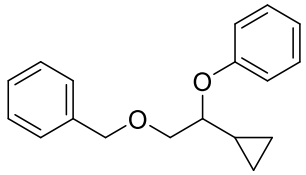
((2-Cyclopropyl-2-isopropoxyethoxy)methyl)benzene (3.23n)



Cyclopropane **3.23n** was synthesized using general procedure F and isopropanol as the alcohol. The crude was purified by a flash column chromatography (2% diethyl ether/hexanes) on silica gel to afford a colorless liquid (26.4 mg, 28% yield). **Rf**: 0.29 (10% diethyl ether/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.38-7.35 (m, 4 H, Ph), 7.33-7.30 (m, 1 H, *p*-Ph), 4.62 (d, *J* = 13.9 Hz,

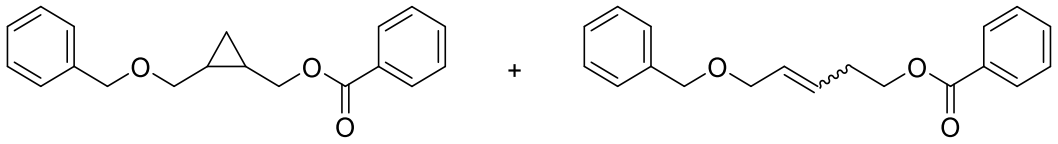
1 H, 1×OC**H**$_2$Ph), 4.60 (d, *J* = 13.9 Hz, 1 H, 1×OC**H**$_2$Ph), 3.85 (hept, *J* = 6.1 Hz, 1 H, C**H**$(CH_3)_2$), 3.60 (dd, *J* = 6.0, 4.3 Hz, 2 H, C**H**$_2$OBn), 2.99 (ddd, *J* = 10.7, 4.6, 3.1 Hz, 1 H, C**H**O*i*-Pr), 1.19 (d, *J* = 6.0 Hz, 3 H, C**H**$_3$), 1.18 (d, *J* = 6.0 Hz, 3 H, C**H**$_3$), 0.92 (dtt, *J* = 8.4, 5.3, 2.6 Hz, 1 H, C**H**$_{cyclopropyl}$), 0.60-0.46 (m, 2 H, 2×C**H**$_{2cyclopropyl}$), 0.37 (sexd, *J* = 4.4, 0.6 Hz, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.24 (hexd, *J* = 4.3, 0.7 Hz, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 138.7 (**C**q, Ph), 128.3 (2×**C**H, Ph), 127.45 (2×**C**H, Ph), 127.42 (**C**H, Ph), 79.7 (**C**HO), 74.2 (O**C**H_2Ph), 73.4 (**C**H_2OBn), 70.3 (**C**H$(CH_3)_2$), 22.8 (**C**H_3), 22.7 (**C**H_3), 13.2 (**C**$H_{cyclopropyl}$), 3.2 (**C**$H_{2cyclopropyl}$), 1.7 (**C**$H_{2cyclopropyl}$). **FTIR** (cm^{-1}) (neat): 3005, 2970, 2829, 2860, 1454, 1378, 1366, 1328, 1203, 1170, 1119, 1088, 1048, 1020, 822, 734, 697. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{15}H_{22}O_2$ $[M+H]^+$: 235.1693, 235.1690.

(2-(Benzyloxy)-1-cyclopropylethoxy)benzene (3.23o)



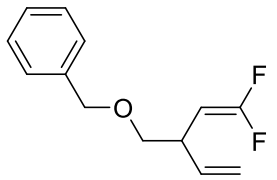
Cyclopropane **3.23o** was synthesized using general procedure F and phenol (0.4 M in CH_2Cl_2) as the alcohol. The crude was purified by a flash column chromatography (2% diethyl ether/hexanes) on silica gel to afford a colorless liquid (23.3 mg, 22% yield). **Rf**: 0.32 (10% diethyl ether/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.39-7.31 (m, 5 H, Ph), 7.31-7.30 (m, 2 H, Ph), 7.00-6.95 (m, 3 H, Ph), 4.62 (s, 2 H, OC**H**$_2$Ph), 3.97 (dt, *J* = 7.4, 5.1 Hz, 1 H, C**H**O), 3.77 (s, 1 H, 1×C**H**$_2$OBn), 3.76 (d, *J* = 1.0 Hz, 1×C**H**$_2$OBn), 1.19 (dtt, *J* = 8.1, 5.0, 3.1 Hz, 1 H, C**H**$_{cyclopropyl}$), 0.58-0.57 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.56-0.55 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.45-0.39 (m, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.38-0.33 (m, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 158.9 (**C**q), 138.3 (**C**q), 129.4 (2×**C**H), 128.4 (2×**C**H), 128.35 (2×**C**H), 128.31 (2×**C**H), 127.56 (2×**C**H), 127.55 (2×**C**H), 121.2 (**C**H), 116.9 (CH), 81.3 (O**C**HPh), 73.45 (O**C**H_2Ph), 72.5 (**C**H_2OBn), 12.9 (**C**$H_{cyclopropane}$), 2.8 (**C**$H_{2cyclopropane}$), 1.9 (**C**$H_{2cyclopropane}$). **FTIR** (cm^{-1}) (neat): 3085, 3064, 3028, 3008, 2917, 2858, 1597, 1587, 1492, 1454, 1238, 1119, 1092, 1079, 1027, 751, 737, 694. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{18}H_{20}O_2$ $[M+H]^+$: 286.1802, found 286.1798.

(2-((Benzyloxy)methyl)cyclopropyl)methyl benzoate (3.27p) and 5-(benzyloxy)pent-3-en-1-yl benzoate (3.28)



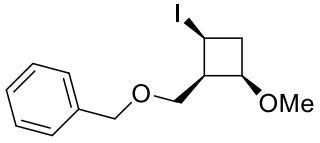
Compounds **3.27p** and **3.28** were synthesized using general procedure F and benzoic acid (0.40 M in CH_2Cl_2) as the alcohol. The crude was purified by a flash column chromatography (5% diethyl ether/hexanes) on silica gel to afford an inseparable mixture of **3.27p** (35.9 mg, 20% yield) and **3.28** (22.1 mg, 13% yield) in a 1.6:1 ratio and as a colorless liquid. **Rf**: 0.21 (10% diethyl ether/hexanes). *Major isomer*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.59-7.55 (m, 2 H, Ph), 7.46-7.42 (m, 1 H, Ph), 7.36-7.29 (m, 7 H, Ph), 4.56 (d, *J* = 11.8 Hz, 1×OC**H**$_2$Ph), 4.51 (d, *J* = 11.6 Hz, 1×OC**H**$_2$Ph), 4.48 (dd, *J* = 11.9, 7.2 Hz, 1 H, 1×C**H**$_2$OBz), 4.29 (dd, *J* = 11.8, 8.0 Hz, 1 H, 1×C**H**$_2$OBz), 3.69 (dd, *J* = 10.4, 6.4 Hz, 1 H, 1×C**H**$_2$OBn), 3.50 (dd, *J* = 10.4, 8.0 Hz, 1 H, 1×C**H**$_2$OBn), 1.52-1.44 (m, 1 H, C**H**$_{cyclopropyl}$CH$_2$OBz), 1.43-1.36 (m, 1 H, C**H**$_{cyclopropyl}$CH$_2$OBn), 0.94 (td, *J* = 8.4, 5.1 Hz, 1 H, 1×C**H**$_{2cyclopropyl}$), 0.41 (q, *J* = 5.5 Hz, 1 H, 1×C**H**$_{2cyclopropyl}$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 166.7 (**C**O$_2$), 138.3 (**C**qCO), 132.8 (**C**H, Ph), 130.5 (**C**q, Ph) 129.64 (**C**H, Ph), 128.4 (2×**C**H, Ph), 128.3 (2×**C**H, Ph), 127.8 (2×**C**H, Ph), 127.7 (2×**C**H, Ph), 72.9 (O**C**H$_2$Ph), 70.0 (**C**H$_2$OBn), 65.3 (**C**H$_2$OBz), 15.8 (**C**H$_{cyclopropyl}$CH$_2$OBn) 15.5 (**C**H$_{cyclopropyl}$CH$_2$OBz), 8.6 (**C**H$_{2cyclopropyl}$). *Minor isomer*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.59-7.55 (m, 2 H, Ph), 7.46-7.42 (m, 1 H, Ph), 7.36-7.29 (m, 7 H, Ph), 5.83-4.77 (m, 1 H, =C**H**CH$_2$O), 5.74-5.68 (m, 1 H, =C**H**CH$_2$CH$_2$O), 4.53 (s, 2 H, OC**H$_2$**Ph), 4.36 (t, *J* = 6.7 Hz, 2 H, C**H$_2$**OBz), 4.15 (dd, *J* = 6.4, 0.7 Hz, 2 H, =CHC**H$_2$**O), 2.57 (qd, *J* = 5.9, 1.0 Hz, 2 H, =CHC**H$_2$**CH$_2$O). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 166.6 (**C**O$_2$), 138.2 (**C**qCO), 132.9 (**C**H, Ph), 130.2 (**C**q, Ph), 129.57 (**C**H, Ph), 129.1 (=**C**HCH$_2$O), 128.45 (=**C**HCH$_2$CH$_2$O), 128.41 (2×**C**H, Ph), 128.37 (2×**C**H, Ph), 127.66 (2×**C**H, Ph), 127.58 (2×**C**H, Ph), 72.3 (O**C**H$_2$Ph), 65.7 (=CH**C**H$_2$O), 64.0 (**C**H$_2$OBz), 27.4 (**C**H$_2$CO$_2$). **FTIR** (cm^{-1}) (neat): 2956, 2870, 2822, 1722 (C=O), 1444, 1362, 1192, 1085, 1024, 963, 739, 691, 603. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{19}H_{20}O_3$ [M+Na]$^+$: 319.1310, found 319.1312.

(((4,4-Difluoro-2-vinylbut-3-en-1-yl)oxy)methyl)benzene (3.29)



In a flame-dried 5 mL microwave vial, anhydrous sodium iodide (18.0 mg, 0.12 mmol, 20% mol) was added to bicyclo(1.1.0)butane **3.22a** (105 mg, 0.6 mmol, 1.0 equiv) in THF (1.5 mL, 0.40 M) to give a yellow solution. Trifluoromethyltrimethylsilane (220 uL, 1.5 mmol, 2.5 equiv) was added dropwise and the reaction mixture stirred at room temperature during 60 minutes. The reaction mixture was filtered over cotton, the volatiles were removed under reduced pressure and the residue was purified by flash chromatography (5% diethyl ether /hexanes) to afford **3.29** as a colorless liquid (45.7 mg, 37% yield). **Rf**: 0.59 (10% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.40-7.31 (m, 5 H, Ph), 5.85 (ddd, *J* = 17.1, 10.4, 6.3 Hz, 1 H, C**H**=CH_2), 5.17 (dt, *J* = 17.1, 1.4 Hz, 1 H, 1×=C**H**$_2$), 5.14 (dt, *J* = 10.4, 1.3 Hz, 1 H, 1×=C**H**$_2$), 4.57 (s, 2 H, OC**H$_2$**Ph), 4.26 (ddd, *J* = 25.4, 9.6, 2.7 Hz, 1 H, C**H**=CF_2), 3.48 (dd, *J* = 6.2, 0.7 Hz, 2 H, C**H**$_2$OBn), 3.34-3.23 (m, 1 H, C**H**CH_2OBn). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 156.6 (dd, *J* = 288.4, 286.7 Hz, =**C**F_2), 138.2 (C**H**=CH_2), 137.1 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.7 (**C**H, Ph), 127.6 (2×**C**H, Ph), 115.9 (**C**H_2=CH), 78.2 (dd, *J* = 22.5, 19.7 Hz, **C**H=CF_2), 73.0 (O**C**H_2Ph), 72.9 (t, *J* = 2.2 Hz, **C**H_2CHCH=CF_2), 38.1 (d, *J* = 4.6 Hz, **C**HCH=CF_2). **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm –87.26 (d, *J* = 43.8 Hz, 1 F), –89.25 (dd, *J* = 43.8, 25.4 Hz, 1 F). **FTIR** (cm^{-1}) (neat): 2858, 1743, 1642, 1496, 1454, 1361, 1271, 1186, 1099, 1028, 992, 961, 916, 816, 735, 697, 605, 466. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{14}F_2O$ $[M+Ag]^+$: 331.0058, found 331.0049.

((((1*R,2*R**,4*R**)-2-iodo-4-methoxycyclobutyl)methoxy)methyl)benzene (3.32)**

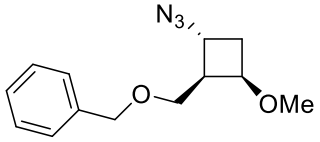


In a flame-dried 5 mL microwave vial, a fresh solution of recrystallized *N*-iodosuccinimide (0.9 mL, 1.0 M in distilled THF, 1.1 equiv) was added to crude BCB **3.22a** (139 mg, 0.8 mmol, 1.0 equiv) in methanol (4 mL, 0.20 M) at room temperature and the reaction mixture was stirred during 30 minutes. The reaction mixture was quenched with a saturated solution of sodium

bicarbonate and the cyclobutane was extracted from the aqueous layer by washing with diethyl ether (3×5 mL). The combined organic layers were washed successively with saturated solution of sodium sulfate and brine, dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (0-5% diethyl ether/hexanes) to afford **3.32** as a single diastereomer and a colorless liquid (205.1 mg, 77% yield). **Rf**: 0.63 (10% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.44-7.40 (m, 2 H, *o*-Ph), 7.37 (dd, *J* = 7.2, 1.8 Hz, 2 H, *m*-Ph), 7.31 (tt, *J* = 7.2, 1.1 Hz, 1 H, *p*-Ph), 4.65 (d, *J* = 11.6 Hz, 1 H, OC**H**$_2$Ph), 4.58 (d, *J* = 11.6 Hz, 1 H, OC**H**$_2$Ph), 4.25 (dt, *J* = 9.6, 7.8 Hz, 1 H, C**H**I), 4.00 (dd, *J* = 13.9, 6.8 Hz, 1 H, C**H**OMe), 3.92 (dd, *J* = 9.7, 7.1 Hz, 1 H, C**H**$_2$OBn), 3.67 (dd, *J* = 9.7, 6.3 Hz, 1 H, C**H**$_2$OBn), 3.31 (s, 3 H, OC**H**$_3$), 3.06-2.93 (m, 2 H, C**H**$_{cyclobutyl}$CH$_2$OBn,1×C**H**$_{2cyclobutyl}$), 2.60-2.53 (m, 1 H, 1×C**H**$_{2cyclobutyl}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.4 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.9 (2×**C**H, Ph), 127.6 (**C**H, Ph), 74.2 (**C**H$_{cyclobutyl}$OMe), 73.5 (O**C**H$_2$Ph), 72.2 (**C**H$_2$OBn), 57.1 (O**C**H$_3$), 46.0 (**C**H$_{cyclobutyl}$), 42.8 (**C**H$_{2cyclobutyl}$), 11.7 (**C**HI). **FTIR** (cm^{-1}) (neat): 2983, 2933, 2879, 2860, 2829, 1496, 1453, 1363, 1217, 1114, 1029, 834, 737, 698. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{17}IO_2$ [M+Na]$^+$: 355.0165, found 355.0167.

Note: NIS must be free of HI and freshly recrystallized from dioxane/CCl_4.

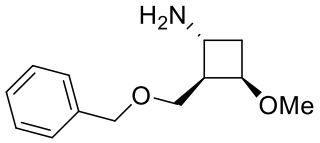
((((1*R,2*S**,4*R**)-2-Azido-4-methoxycyclobutyl)methoxy)methyl)benzene (3.33)**



In a flame-dried 10 mL round bottom flask, sodium azide (173 mg, 2.5 mmol, 2.5 equiv) was added to iodocyclobutane **3.32** (332 mg, 1.0 mmol, 1.0 equiv) in DMF (5 mL, 0.2 M) under argon. The reaction mixture was heated to 80 °C in an oil bath and stirred during 18 hours. The mixture was allowed to cool down to room temperature, then water (5 mL) was added. The cyclobutane was extracted from the aqueous layer by washing with diethyl ether (3×5 mL) and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure to afford cyclobutylazide **3.33** as a yellow liquid (240.2 mg, 97%), which was used without purification for next step. **Rf**: 0.30 (10% ethyl acetate/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.38-7.37 (m, 4 H, Ph), 7.33-7.31 (m, 1 H, *p*-Ph), 4.57 (d, *J* = 18.0 Hz,

1 H, 1×OC**H₂**Ph), 4.55 (dd, *J* = 18.0 Hz, 1 H, 1×OC**H₂**Ph), 4.04 (td, *J* = 7.6, 2.7 Hz, 1 H, $C_{cyclobutyl}$**H**N_3), 3.87 (dd, *J* = 14.8, 7.2 Hz, 1 H, $C_{cyclobutyl}$**H**OMe), 3.74 (dd, *J* = 9.6, 7.6 Hz, 1 H, 1×C**H₂**OBn), 3.59 (dd, *J* = 9.7, 7.2 Hz, 1 H, 1×C**H₂**OBn), 3.28 (s, 3 H, OC**H₃**), 2.80 (quintt, *J* = 7.2, 0.9 Hz, 1 H, $C_{cyclobutyl}$**H**CH_2OBn), 2.33 (dddd, *J* = 12.8, 8.2, 2.8, 0.6 Hz, 1 H, 1×$C_{cyclobutyl}$**H₂**), 2.16 (dtd, *J* = 13.5, 6.8, 1.7 Hz, 1 H, 1×$C_{cyclobutyl}$**H₂**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.3 (**C**q, Ph), 128.4 (2×**C**H, Ph), 127.7 (2×**C**H, Ph), 127.6 (**C**H, *p*-Ph), 73.2 (O**C**H_2Ph), 72.7 (**C**$_{cyclobutyl}$$HN_3$), 66.9 (**C**$H_2$OBn), 56.8 (O**C**$H_3$), 56.3 (**C**$_{cyclobutyl}$HOMe), 47.5 (**C**$_{cyclobutyl}$$HCH_2$OBn), 33.3 (**C**$_{cyclobutyl}$$H_2$). **FTIR** ($cm^{-1}$) (neat): 2930, 2097 (N=N=N), 1496, 1454, 1365, 1341, 1261, 1216, 1097, 1028, 737, 698, 605, 469. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{17}N_3O_2$ $[M+Ag]^+$: 354.0366, found 354.0358.

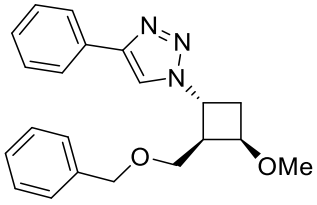
(1*S,2*R**,3*R**)-2-((benzyloxy)methyl)-3-methoxycyclobutan-1-amine (3.34)**



In a 10 mL round bottom flask, triphenylphosphine (315 mg, 1.20 mmol, 2.0 equiv), then hydrochloric acid 5 M (2.52 mL, 12.6 mmol, 20.0 equiv) were successively added to cyclobutylazide **3.33** (148 mg, 0.60 mmol, 1.0 equiv) in THF (2.00 mL) at room temperature. After 2 hours, saturated Na_2CO_3 (aq) was added and the cyclobutane was extracted from the aqueous layer by washing with ethyl acetate (3×5 mL). Combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford aminocyclobutane **3.34** (85.5 mg, 64%) as a brown oil. **Rf**: 0.30 (10% MeOH/CH_2Cl_2). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.38-7.35 (m, 4 H, Ph), 7.32-7.30 (m, 1 H, *p*-Ph), 4.56 (d, *J* = 17.2 Hz, 1 H, 1×C**H₂**Ph), 4.53 (d, *J* = 17.2 Hz, 1 H, 1×C**H₂**Ph), 4.02 (td, *J* = 6.4, 2.4 Hz, 1 H, $C_{cyclobutyl}$**H**N) 3.74 (td, *J* = 8.3, 0.9 Hz, 1 H, C**H₂**OBn), 3.60 (dd, *J* = 9.6, 7.0 Hz, 1 H, $C_{cyclobutyl}$**H**OMe), 3.28 (s, 3 H, OC**H₃**), 2.47 (ddt, *J* = 6.9, 6.8, 6.7 Hz, 1 H, $C_{cyclobutyl}$**H**CH_2OBn), 2.32-2.27 (m, 1 H, 1×$C_{cyclobutyl}$**H₂**), 2.05 (br s, 2 H, N**H₂**) 1.88 (dt, *J* = 13.1, 6.9 Hz, 1 H, 1×$C_{cyclobutyl}$**H₂**). **^{13}C NMR** (126 MHz, CD_3OD) δ ppm 138.2 (**C**q, Ph), 128.0 (2×**C**H, Ph), 127.3 (2×**C**H, Ph), 127.4 (**C**H, *p*-Ph), 72.6 (O**C**H_2Bn), 72.5 (**C**H-N), 66.8 (**C**H_2OBn), 55.7 (O**C**H_3), 47.6 (**C**$H_{cyclobutyl}$-CH_2OBn), 33.1 (**C**$_{cyclobutyl}$$H_2$). **FTIR** ($cm^{-1}$) (neat):

2926, 2856, 1454, 1365, 1100, 1074, 740, 699, 459. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{13}H_{19}NO_2$ $[M+H]^+$: 222.1489, found 222.1492.

1-((1*S,2*R**,3*R**)-2-((Benzyloxy)methyl)-3-methoxycyclobutyl)-4-phenyl-1H-1,2,3-triazole (3.35)**

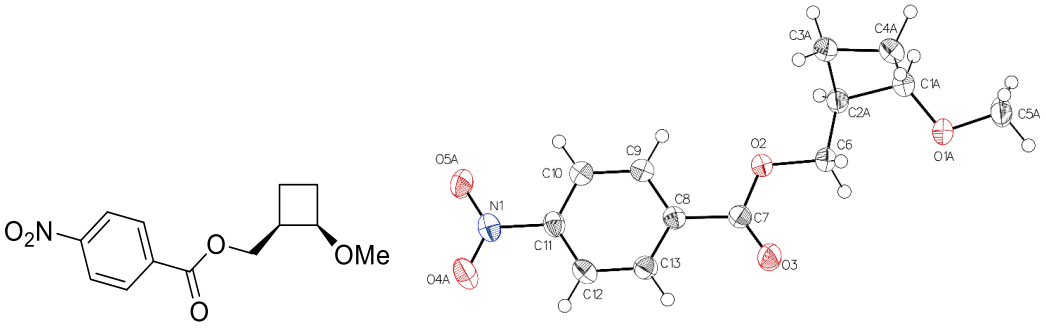


In a 5 mL flame-dried microwave vial, copper (I) iodide (5.0 mg, 0.03 mmol, 25 mol%) was added to cyclobutylazide **3.33** (24.7 mg, 0.10 mmol, 1.0 equiv) in THF (1.0 mL, 0.10 M) to give a white suspension. Triethylamine (0.03 mL, 0.20 mmol, 2.0 equiv) and phenylacetylene (0.02 mL, 0.15 mmol, 1.5 equiv) were successively added and the reaction mixture turned yellow. The reaction mixture was stirred at room temperature during 18 hours. The mixture was filtered over celite, rinsed with CH_2Cl_2 and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate/hexanes) to afford cyclobutane **3.35** (31.9 mg, 91%) as white needles. **mp**. 63 °C. **Rf**: 0.25 (30% ethyl acetate/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.85 (s, 1 H, $C_{triazole}$**H**), 7.77 (dt, *J* = 7.1, 5.5 Hz, 2 H, Ph), 7.43 (tt *J* = 7.3, 1.6 Hz, 3 H, Ph) 7.36-7.32 (m, 6 H, Ph), 4.96 (ddd, $J_1 = J_2 = J_3$ = 7.8 Hz, 1 H, $C_{cyclobutyl}$**H**OMe), 4.55 (s, 2 H, OC**H$_2$**Ph), 4.21 (td, *J* = 6.5, 2.3 Hz, 1 H, $C_{cyclobutyl}$**H**N), 3.87 (dd, *J* = 9.9, 6.8 Hz, 1 H, 1×C**H$_2$**OBn), 3.82 (dd, *J* = 9.9, 6.8 Hz, 1 H, 1×C**H$_2$**OBn), 3.37 (s, 3 H, OC**H$_3$**), 3.27 (quintt, *J* = 7.4, 1.0 Hz, 1 H, $C_{cyclobutyl}$**H**-CH_2OBn), 2.94 (quintt, *J* = 6.5, 1.3 Hz, 1 H, 1×$C_{cyclobutyl}$**H$_2$**), 2.70 (dddd, *J* = 13.1, 8.7, 2.2, 0.5 Hz, 1 H, 1×$C_{cyclobutyl}$**H$_2$**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 147.6 (**C**$q_{triazole}$-Ph), 138.1 (**C**q, Ar), 130.7 (**C**q, Ar), 128.8 (2×**C**H, Ph), 128.5 (2×**C**H, Ph), 128.0 (**C**H, Ph), 127.8 (2×**C**H, Ph), 125.7 (2×**C**H, Ph), 119.6 (**C**$_{triazole}$H), 73.3 (O**C**H_2Ph), 73.0 (**C**HN), 67.3 (**C**H_2OBn), 56.9 ($C_{cyclobutyl}$HOMe), 55.9 (O**C**H_3), 48.1 ($C_{cyclobutyl}$HCH_2OBn), 33.4 ($C_{cyclobutyl}$$H_2$). **FTIR** ($cm^{-1}$) (neat): 3031, 2927, 1455, 1347, 1212, 1112, 1075, 1028, 974, 820, 695, 515, 461. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{21}H_{23}N_3O_2$ $[M+H]^+$: 350.1863, found 350.1848.

7.2.5 X-Ray Crystallographic Data

((1*R**,2*R**)-2-Methoxycyclobutyl)methyl 4-nitrobenzoate (3.26)

The data for **3.26** cha240(2), crystallized from diethyl ether/hexanes, were collected from a shock-cooled single crystal at 100 K on a Bruker Smart APEX three-circle diffractometer with a Microfocus Source using Quazar MX Mirror Optics as monochromator and a Bruker APEX2 CCD detector. The diffractometer was equipped with an Oxford Cryostream 700 low temperature device and used Cu Kα radiation (λ = 1.54178 Å). All data were integrated with *SAINT* and a multi-scan absorption correction using *SADABS* was applied.[196] The structure was solved by dual methods using XT and refined by full-matrix least-squares methods against F^2 by *XL*.[197,198] Structure solution and refinement cycles were performed within the graphical user interface of *OLEX2*.[199] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their U_{iso} values constrained to 1.5 times the U_{eq} of their pivot atoms for terminal sp^3 carbon atoms and 1.2 times for all other carbon atoms. Disordered moieties were refined using bond lengths restraints while for the displacement parameter the refinement used a combination of restraints and constraints. This report and the CIF file were generated using FinalCif.



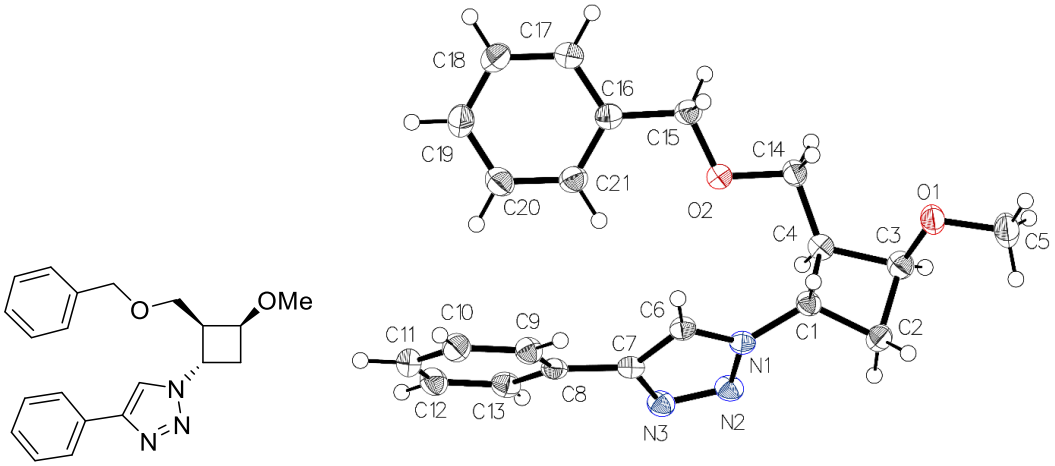
CCDC deposition number	2116653
Empirical formula	$C_{13}H_{15}NO_5$
Formula weight	265.26
Temperature [K]	100
Crystal system	monoclinic
Space group (number)	$P2_1/n$ (14)
a [Å]	6.27910(10)

b [Å]	26.4160(6)
c [Å]	8.3767(2)
α [°]	90
β [°]	109.284(1)
γ [°]	90
Volume [Å^3]	1311.48(5)
Z	4
ρ_{calc} [gcm^{-3}]	1.343
μ [mm^{-1}]	0.876
F(000)	560
Crystal size [mm^3]	0.31×0.15×0.09
Crystal color	clear light colorless
Crystal shape	Plate
Radiation	Cu K_α (λ=1.54178 Å)
2Θ range [°]	6.69 to 144.20a (0.81 Å)
Index ranges	-7 ≤ h ≤ 7 -32 ≤ k ≤ 32 -10 ≤ l ≤ 10
Reflections collected	18080
Independent reflections	2574 R_{int} = 0.0326 R_{sigma} = 0.0175
Completeness to Θ = 67.679°	99.9 %
Data / Restraints / Parameters	2574/182/230
Goodness-of-fit on F^2	1.084
Final R indexes [I≥2σ(I)]	R_1 = 0.0494 wR_2 = 0.1235

Final *R* indexes	$R_1 = 0.0516$
[all data]	$wR_2 = 0.1250$
Largest peak/hole [eÅ^{-3}]	0.36/-0.28

1-((1*S,2*R**,3*R**)-2-((Benzyloxy)methyl)-3-methoxycyclobutyl)-4-phenyl-1H-1,2,3-triazole (3.35)**

The data for **3.35** cha256(2), crystallised from diethyl ether/hexanes, were collected from a shock-cooled single crystal at 150 K on a Bruker Venture Metaljet κ-geometry diffractometer with a Metal Jet using Helios MX Mirror Optics as monochromator and a Bruker CMOS Photon III detector. The diffractometer was equipped with an Oxford Cryostream 700 low temperature device and used Ga Kα radiation (λ = 1.34139 Å). All data were integrated with *SAINT* (2020) and a multi-scan absorption correction using *SADABS* 2016/2 was applied.[196] The structure was solved by dual methods with XT and refined by full-matrix least-squares methods against F^2 using XL.[197,198] Structure solution and refinement cycles were performed within the graphical user interface of *OLEX2*.[199] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their U_{iso} values constrained to 1.5 times the U_{eq} of their pivot atoms for terminal sp^3 carbon atoms and 1.2 times for all other carbon atoms. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre.[199] This report and the CIF file were generated using FinalCif.



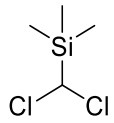
CCDC deposition number	2175205
Empirical formula	$C_{21}H_{23}N_3O_2$
Formula weight	349.42
Temperature [K]	150
Crystal system	monoclinic
Space group (number)	$P2_1/n$ (14)
a [Å]	15.3404(6)
b [Å]	5.5177(2)
c [Å]	21.3195(8)
α [°]	90
β [°]	97.548(2)
γ [°]	90
Volume [Å^3]	1788.93(12)
Z	4
ρ_{calc} [gcm^{-3}]	1.297
μ [mm^{-1}]	0.431
F(000)	744
Crystal size [mm^3]	0.02×0.02×0.4
Crystal color	clear light colorless
Crystal shape	needle
Radiation	Ga K_α (λ=1.34139 Å)
2Θ range [°]	6.61 to 111.83 (0.81 Å)
Index ranges	-18 ≤ h ≤ 18 -6 ≤ k ≤ 6 -26 ≤ l ≤ 25
Reflections collected	16661
Independent reflections	3493 R_{int} = 0.0331 R_{sigma} = 0.0309
Completeness to θ = 53.594°	100.0 %

Data / Restraints / Parameters	3493 / 0 / 236
Goodness-of-fit on F^2	1.054
Final R indexes	$R_1 = 0.0379$
[$I \geq 2\sigma(I)$]	w$R_2 = 0.0936$
Final R indexes	$R_1 = 0.0551$
[all data]	w$R_2 = 0.1021$
Largest peak/hole [eÅ^{-3}]	0.19/−0.20

7.3 Experimental Section of Chapter 4

7.3.1 Experimental Procedure and Characterization Data for the Synthesis of (Diiodo(trimethylsilyl)methyl)boronic Ester and derivatives

(Dichloromethyl)trimethylsilane (4.16a)



In a flame dried three-necked 500 mL round bottom flask, anhydrous dichloromethane (6.0 mL, 93.6 mmol, 1.23 equiv) and anhydrous THF (120 mL, 0.63 M) were added. The mixture was cooled down to –100 °C (EtOH/liquid N_2 bath), then *n*-butyllithium (30.5 mL, 76.1 mmol, 1.00 equiv, 2.5 M solution /hexanes) was added dropwise *via* an addition funnel. The reaction was stirred for 40 min at this temperature, then chlorotrimethylsilane (10 mL, 79.9 mmol, 1.05 equiv) was added in one portion and the reaction was stirred another 40 min at –100 °C, then warmed up to room temperature in a water bath and stirred 60 minutes. Water (75 mL) was added and silane **4.16a** was extracted from the aqueous layer by washing with diethyl ether (3×75 mL). Organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and the volatiles were carefully removed under reduced pressure to afford the desired silane **4.16a** (9.8 g, 85%) as a yellowish liquid and used as is for next step. The characterization data were identical in all respect to those reported in the literature.[200] **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 5.31 (s, 1 H, C**H**Cl_2), 0.26 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 63.7 (**C**HCl_2), –4.1 (Si(**C**H$_3$)$_3$).

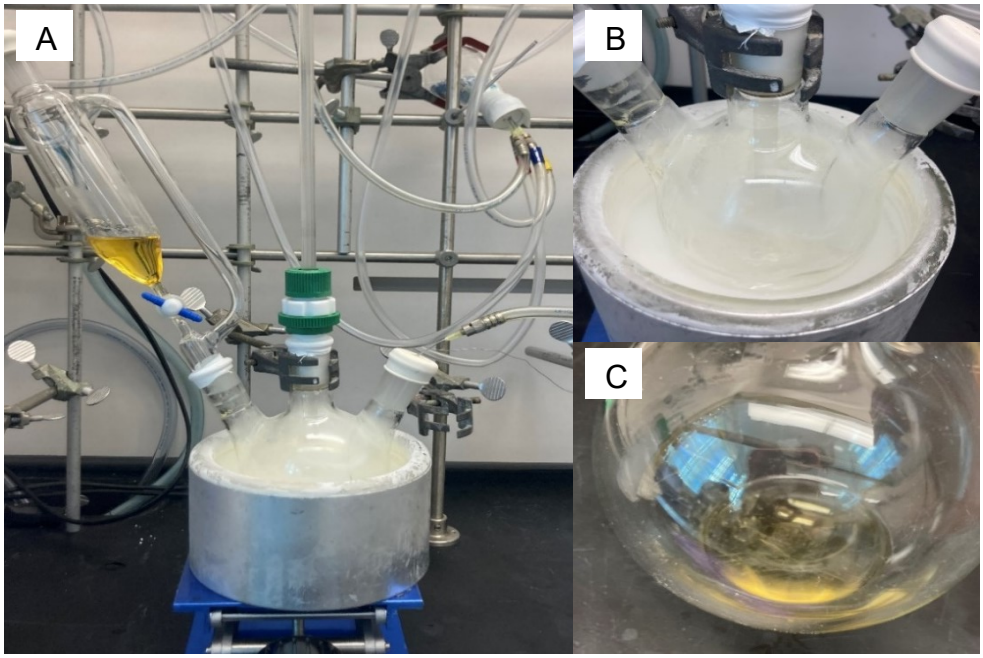
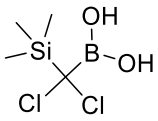


Figure 7.1 Graphical supporting information for the synthesis of (dichloromethyl)trimethylsilane

(A) Set up of the reaction. (B) Reaction mixture after the addition of *n*-BuLi. (C) Crude (dichloromethyl)trimethylsilane

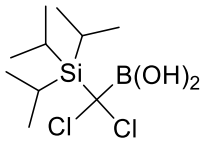
(Dichloro(trimethylsilyl)methyl)boronic acid (4.17a)



In a flame dried three-necked 500 mL round bottom flask, was added (dichloromethyl)trimethylsilane **4.16a** (9.73 g, 61.9 mmol, 1.05 equiv) in THF (103 mL, 0.60 M).[201] The mixture was cooled down to –100 °C (EtOH/liquid N_2 bath), then *n*-butyllithium (23.5 mL 58.8 mmol, 1.0 equiv, 2.5 M solution /hexanes) was added dropwise *via* an addition funnel. The reaction was stirred for 40 min at this temperature, then trimethyl borate (7.32 mL, 65.0 mmol, 1.10 equiv) was added in one portion and the reaction was stirred another 40 min at – 100 °C. The reaction was quenched with 5 M HCl solution (15 mL, 73.1 mmol, 1.18 equiv), the cooling bath was removed and the mixture was stirred at room temperature for 60 minutes. Water (75 mL) was added and boronic acid **4.17a** was extracted from the aqueous layer by washing with ether (3×100 mL). Organic layers were combined, washed with brine, dried over magnesium

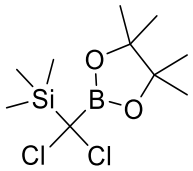
sulfate, filtered and concentrated under reduced pressure to provide the crude boronic acid **4.17a** (11.2 g, 95%) as a colorless oil which was used without purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.30 (s, 3 H, Si(C**H**$_3$)$_3$), 0.27 (s, 6 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm –2.11 Si(**C**H_3)$_3$), the carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 29.1. **FTIR** (cm^{-1}) (neat): 3549, 2961, 2903, 1413, 1284, 1252, 847, 727. Compound **4.17a** was unstable under various ionization techniques and HRMS could not be obtained.

(Dichloro(triisopropylsilyl)methyl)boronic acid (4.17c)



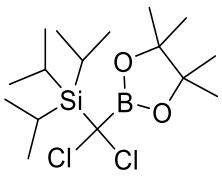
In a flame dried 25 mL round bottom flask, was added (dichloromethyl)triisopropylsilane[170] **4.16c** (725 mg, 3.0 mmol, 1.00 equiv) in THF (5 mL, 0.6 M). The mixture was cooled down to –100 °C (EtOH/liquid N_2 bath), then *n*-butyllithium (1.25 mL 3.1 mmol, 1.05 equiv, 2.5 M solution in hexanes) was added dropwise using a syringe. The reaction was stirred for 40 min at this temperature, then trimethyl borate (0.37 mL, 3.3 mmol, 1.10 equiv) was added in one portion and the reaction was stirred another 40 min at –100 °C. The reaction was quenched with 5 M HCl solution (0.7 mL, 3.5 mmol, 1.20 equiv), the cooling bath was removed and the mixture was stirred at room temperature for 60 minutes. Water was added and boronic acid **4.17c** was extracted from the aqueous layer by washing with ether three times. Organic layers were combined, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide the crude boronic acid **4.17c** (850 mg, 99%) as a colorless oil which was used without purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.39 (s, 3 H, Si(C**H**)$_3$) 1.13 (s, 9 H, 3×C**H**$_3$), 1.11 (s, 9 H, 3×C**H**$_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 62.6 (**C**q), 19.2 (6×**C**H_3) 11.9 (3×**C**H). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 28.8. **FTIR** (cm^{-1}) (neat): 2946, 2893, 2869, 1464, 1403, 1386, 1367, 1264, 1066, 1021, 1005, 920, 883, 802, 675, 644. **HRMS** (ESI, Neg) *m/z*: calcd for $C_{10}H_{23}{}^{11}BCl_2O_2Si$ $[M+H]^-$: 282.0901; found 282.0915.

(Dichloromethyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane (4.18a)



In a flame dried 100 mL round bottom flask, magnesium sulfate (7.05 g, 58.5 mmol, 1.05 equiv) was added to (dichloro(trimethylsilyl)methyl)boronic acid **4.17a** (11.2 g, 55.7 mmol, 1.00 equiv) in dichloromethane (45 mL, 1.2 M). Pinacol (6.65 g, 55.7 mmol, 1.00 equiv) was added and the reaction was stirred at room temperature for 16 hours. The reaction mixture was filtered over a pad of celite using a frittered funnel and the volatiles were removed under reduced pressure to obtain the crude boronic ester **4.18a** (855 mg, 97%) as a white solid. The product can be purified by recrystallization in hexanes if needed or used without further purification. **mp**: 58-60 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.34 (s, 12 H, 4×C_{pin}**H**$_3$), 0.28 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 85.4 (2×O**C**q), 24.6 (4×**C**$_{pin}$H$_3$), –3.7 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (160 MHz, $CDCl_3$) δ ppm 30.7. **FTIR** (cm^{-1}) (neat): 2988, 2927, 1738, 1698, 1393, 1373, 1344, 1320, 1270, 1252, 1144, 974, 848, 719. Compound **4.18a** was unstable under various ionization techniques and HRMS could not be obtained.

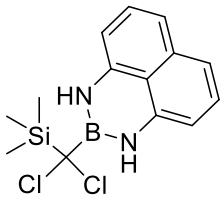
(Dichloro(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)triisopropylsilane (4.18c)



In a flame dried 10 mL round bottom flask, magnesium sulfate (397 mg, 3.15 mmol, 1.1 equiv) was added to boronic acid **4.17c** (850 mg, 3.00 mmol, 1.0 equiv) in dichloromethane (2.5 mL, 1.2 M). Pinacol (360 mg, 3.00 mmol, 1.0 equiv) was added and the reaction was stirred at room temperature for 16 hours. The reaction mixture was filtered over a pad of celite using a frittered funnel and the volatiles were removed under reduced pressure to obtain crude boronic ester **4.18c** (1.05 g, 96%) as a white solid. The product can be purified by recrystallization in hexanes if needed or used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.53 (sept, J = 7.6 Hz,

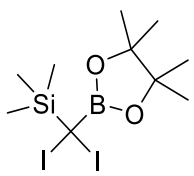
3 H, 3×C**H**$(CH_3)_2$), 1.34 (s, 4×Cpin**H$_3$**, 12 H), 1.22 (d, *J* = 7.5 Hz, 18 H, 6×C**H$_3$**). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 85.3 (2×O**C**q), 24.6 (2×**C**pinH_3), 19.2 (6×**C**H_3), 11.6 (3×**C**H). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 30.4. **FTIR** (cm^{-1}) (neat): 2978, 2945, 2892, 2869, 1466, 1372, 1321, 1339, 1269, 1140, 1111, 971, 883, 849, 667, 626, 560. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{16}H_{33}{}^{11}BCl_2O_2Si$ $[M+NH_4]^+$: 384.2062; found 384.2075.

2-(Dichloro(trimethylsilyl)methyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (4.18f)



In a flame dried 10 mL round bottom flask, magnesium sulfate (600 mg, 5.0 mmol, 1.1 equiv) was added to boronic acid **4.17a** (1.0 g, 5.0 mmol, 1.0 equiv) in toluene (5.0 mL, 1 M). 1,8-diaminonaphthalene (796 mg, 5.0 mmol, 1.0 equiv) was added and the reaction was stirred at 110 °C in an oil bath during for 16 hours. The reaction mixture was filtered over a pad of celite using a frittered funnel, rinsed with ethyl acetate and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (30% CH_2Cl_2/hexanes) to afford **4.18f** (545 mg, 34 %) as a white solid. **mp**: 158 °C. **Rf**: 0.11 (10% CH_2Cl_2/hexanes) **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.16 (dd, *J* = 8.4, 7.2 Hz, 2 H, Ar), 7.09 (dd, *J* = 8.4, 0.9 Hz, 2 H, Ar), 6.42 (dd, *J* = 7.3, 1.0 Hz, 2 H, Ar), 0.32 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 140.1 (2×**C**qN), 136.2 (**C**q, Ar), 127.6 (2×**C**H, Ar), 119.64 (**C**q, Ar), 118.5 6 (2×**C**H, Ar), 106.5 6 (2×**C**H, Ar), −3.5 (Si(**C**H_3)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (161 MHz, $CDCl_3$) δ ppm 29.3. **FTIR** (cm^{-1}) (neat): 2978, 2945, 2892, 2869, 1466, 1372, 1321, 1339, 1269, 1140, 1111, 971, 883, 849, 667, 626, 560. Compound **4.18f** was unstable under various ionization techniques and HRMS could not be obtained.

(Diiodo(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane (4.20a)



In a flame-dried 250 mL round bottom flask, sodium iodide (32.4 g, 216 mmol, 4.0 equiv) was added to (dichloro(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane **4.18a** (15.3 g, 54 mmol, 1.0 equiv) in freshly distilled acetone (108 mL, 0.50 M). The reaction was vigorously stirred and heated to reflux in an oil bath. After 4 days, the reaction mixture was allowed to cool down to room temperature and a further portion of sodium iodide (32.4 g, 216 mmol, 4.0 equiv) was added. The reaction was heated to reflux in an oil bath for 4 more days or until completion (monitored by ^{1}H NMR). Then reaction was cooled at room temperature and was filtered over a pad of Celite® through a frittered funnel to remove salts. The filtrate was concentrated under reduced pressure and the residue was dissolved in dichloromethane. A magnetic stir bar, magnesium sulfate, then sodium thiosulfate were added and the mixture was shaken until disappearance of the orange color (10-15 minutes), filtered over a pad of Celite® through a frittered funnel and concentrated under reduced pressure to afford the desired product **4.20a** (21.4 g, 85%) as a pale yellow solid. The product can be recrystallized in acetone if needed or used without further purification. **mp**: 114-116 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.31 (s, 12 H, 4×C_{pin}**H**$_3$), 0.34 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 85.2 (2×O**C**q), 24.3 (4×**C**$_{pin}$H$_3$), –1.2 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (160 MHz, $CDCl_3$) δ ppm 31.6. **FTIR** (cm^{-1}) (neat): 2979, 2962, 2930, 2898, 1467, 1372, 1330, 1304, 1266, 1248, 1141, 969, 846, 733, 698, 619, 543. **HRMS** (ESI, Pos) *m/z*: calcd for $C_{10}H_{22}{}^{11}BI_2O_2Si$ $[M+H]^+$: 466.9566; found 466.9566.

7.3.2 Information About Lamps

White LED strips were purchased from CDNLUX©, model MTL-FP8AEHWK-120ACW, CCT: 6000 K. A 60 cm white LEDs strip containing 65 diodes was wrapped inward a 5-cm diameter-metal ring.

7.3.3 General Procedure G: Photochemical *gem*-Borotrimethylsilylcyclopropanation

In a flame-dried 5 mL microwave vial, styrene **4.21a-ac** (0.2 mmol, 1.0 equiv), (TMS)I_2CB(pin) **4.20a** (186 mg, 0.4 mmol, 2.0 equiv), Eosin Y (2.8 mg, 0.004 mmol, 0.02 equiv) and sodium thiosulfate (79 mg, 0.50 mmol, 2.5 equiv) were successively weighed. Acetone (800 µL, 0.25 M) was added to give a yellow suspension. DIPEA (175 µL, 1 mmol, 5.0 equiv) was added to give an orange suspension. Nitrogen gas was bubbled in the reaction for 5 minutes. The

reaction mixture was sealed with parafilm. The apparatus was placed on a stirring plate and the microwave vial in the ring, approximately 2 cm away from the light. The lights were switched on and the reaction mixture was stirred and irradiated under white LEDs for 24 hours. The vial was removed from the lights and the reaction mixture was diluted with CH_2Cl_2 (5 mL), then H_2O (2 mL) and then HCl 2 M (2 mL). Triphenylmethane (10.3 mg, 0.042 mmol, 0.21 equiv) was added as the internal standard. Cyclopropane **4.22a-ac** was extracted from the aqueous layer by washing with CH_2Cl_2 (3×5 mL), dried over magnesium sulfate, filtered over a pad of silica and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography with the assigned solvent system or with silver nitrate impregnated silica the reaction was incomplete to afford cyclopropanes **4.22a**-**ac.**

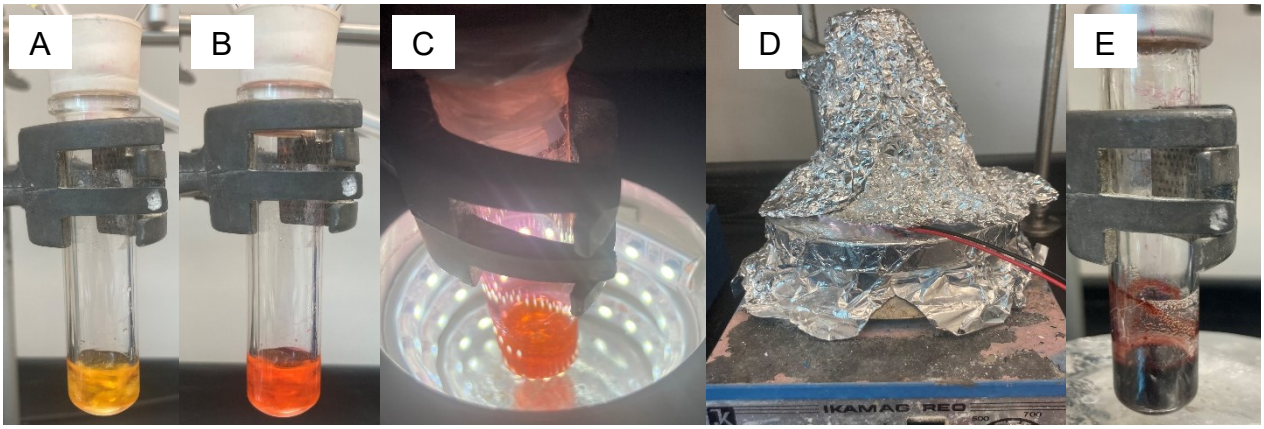


Figure 7.2 Graphical supporting information for setting up the photochemical reaction

Reaction mixture (A) before the addition of DIPEA, (B) after the addition of DIPEA, (C) set up, (D) covered by aluminium foil, (E) after 24 hours under irradiation.

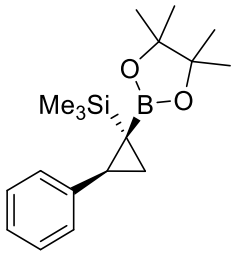
Scale-up procedure for borotrimethylsilylcyclopropanation of 4.21a

In a flame-dried 20 mL microwave vial, (TMS)I_2CB(pin) **4.20a** (466 mg, 1.0 mmol, 1.0 equiv), Eosin Y (6.9 mg, 0.01 mmol, 0.01 equiv) and sodium thiosulfate (395 mg, 2.5 mmol, 2.5 equiv) were successively weighed. Acetone (4.0 mL, 0.25 M), then styrene **4.21a** (0.35 mL, 3 mmol, 3.0 equiv) were successively added to give a yellow suspension. DIPEA (0.9 mL, 5 mmol, 5 equiv) was added to give an orange suspension. Nitrogen gas was bubbled in the reaction for 5 minutes. The apparatus was placed on a stirring plate and the microwave vial in the ring, approximately 2

cm away from the light. The lights were switched on and the reaction mixture was stirred and irradiated under white LEDs for 40 hours. The volatiles were removed under reduced pressure. The reaction mixture was diluted with CH_2Cl_2 (10 mL), then H_2O (5 mL) and HCl 2 M (5 mL) were added. Cyclopropane **4.22a** was extracted from the aqueous layer by washing with CH_2Cl_2 (3×10 mL), dried over magnesium sulfate, filtered over a pad of silica and the volatiles were removed under reduced pressure to afford cyclopropane **4.22a** as a white solid (247 mg, 78% isolated yield, 11:1 dr). The residue can be used as is for next step or purified by flash chromatography (10% CH_2Cl_2/hexanes).

7.3.4 Characterization Data for Borosilylcyclopropanes

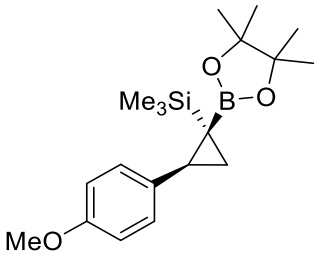
Trimethyl((1*S,2*R**)-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) silane (4.22a)**



Cyclopropane **4.22a** was synthesized using general procedure G, using styrene **4.21a** (20.8 mg, 0.2 mmol) as the starting material and obtained as a white solid (51.2 mg, 89% NMR yield, 81% isolated yield, 11:1 dr). **mp**: 47-49 °C. **Rf**: 0.18 (20% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (700 Hz, $CDCl_3$) δ ppm 7.26-7.21 (m, 4 H, Ph), 7.12 (t, *J* = 7.2 Hz, 1 H, *p*-Ph), 2.14 (dd, *J* = 6.8, 5.4 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.53 (dd, *J* = 4.7, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H_2**), 1.02 (dd, *J* = 7.0, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H_2**), 0.95 (s, 6 H, 2×C_{pin}**H_3**), 0.88 (s, 6 H, 2×C_{pin}**H_3**), 0.08 (s, 9 H, Si(C**H_3**)$_3$). **^{13}C NMR** (176 MHz, $CDCl_3$) δ ppm 141.4 (**C**q, Ph), 128.6 (2×**C**H, Ph), 127.8 (2×**C**H, Ph), 125.7 (**C**H, Ph), 82.6 (2×**C**qO), 25.1 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 12.5 (**C**$_{cyclopropyl}$H$_2$), 3.7 (**C**qBSi), –2.3 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.4. *Minor diastereomer.* **^{1}H NMR** (700 Hz, $CDCl_3$) δ ppm 7.31-7.25 (m, 4 H, Ph), 7.18 (t, *J* = 7.3 Hz, 1 H, *p*-Ph), 2.52 (dd, *J* = 7.3, 5.8 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.29-1.27 (m, 1 H, $C_{cyclopropyl}$**H_2**), 1.26 (s, 6 H, 2×C_{pin}**H_3**), 1.25 (s, 6 H, 2×C_{pin}**H_3**), 1.18 (dd, *J* = 5.2, 3.2 Hz, 1 H, $C_{cyclopropyl}$**H_2**), –0.26 (s, 9 H, Si(C**H_3**)$_3$). **^{13}C NMR** (176 MHz, $CDCl_3$) δ ppm 140.7 (**C**q, Ph), 130.2 (2×**C**H, Ph), 127.7 (2×**C**H, Ph), 126.1 (**C**H, Ph), 84.0 (2×**C**qO), 29.7 (Ar**C**$_{cyclopropyl}$H), 27.4 (2×**C**$_{pin}$H$_3$), 24.6 (2×**C**$_{pin}$H$_3$),

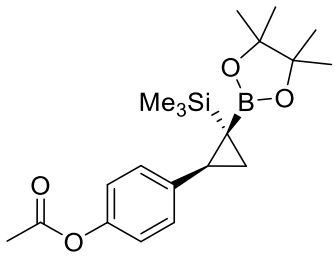
12.3 ($\mathbf{C}_{\text{cyclopropyl}}H_2$), –0.9 (Si($\mathbf{C}H_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **FTIR** (cm^{-1}) (neat): 2977, 2898, 1603, 1496, 1360, 1331, 1302, 1247, 1145, 1118, 959, 880, 849, 838, 759, 696. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{18}H_{30}{}^{11}BO_2Si$ [M+H]$^+$: 317.2102; found 317.2117.

((1*S,2*R**)-2-(4-Methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22b)**



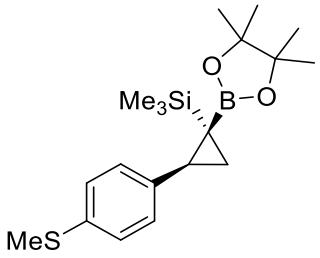
Cyclopropane **4.22b** was synthesized using general procedure G, using 4-methoxystyrene **4.21b** (26.8 mg, 0.2 mmol) as the starting material and obtained as a white solid (66.5 mg, 97% NMR yield, 96% isolated yield, 11:1 dr). **mp**: 37-43 °C. **Rf**: 0.14 (20% CH_2Cl_2/hexanes). *Major diastereomer*. **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.18 (dt, *J* = 8.4, 2.9 Hz, 2 H, Ar), 6.79 (dt, *J* = 8.6, 2.6 Hz, 2H, Ar), 3.78 (s, 3 H, OC**H$_3$**), 2.09 (dd, *J* = 7.0, 5.0 Hz, 1 H, Ar$C_{\text{cyclopropyl}}$**H**), 1.46 (dd, *J* = 5.0, 3.6 Hz, 1 H, 1×$C_{\text{cyclopropyl}}$**H$_2$**), 1.00-0.98 (m, 7 H, 1×$C_{\text{cyclopropyl}}$**H$_2$**, 2×C_{pin}**H$_3$**), 0.89 (s, 6 H, 2×C_{pin}**H$_3$**), 0.07 (s, 9H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 157.8 (**C**q, Ar-OMe), 133.6 (**C**q, Ar), 129.7 (2×**C**H, Ar), 113.3 (2×**C**H, Ar), 82.6 (2×**C**qO), 55.4 (O**C**H$_3$), 24.9 (2×**C**$_{\text{pin}}$H$_3$), 24.4 (2×**C**$_{\text{pin}}$H$_3$), 24.3 (Ar**C**$_{\text{cyclopropyl}}$H), 12.5 (**C**$_{\text{cyclopropyl}}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.0. **FTIR** (cm^{-1}) (neat): 2976, 1514, 1361, 1300, 1245, 1146, 1037, 835. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{18}H_{31}{}^{11}BO_3Si$ [M+H]$^+$: 347.2208; found 347.2216.

4-((1*R,2*S**)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl) phenyl acetate (4.22c)**



Cyclopropane **4.22c** was synthesized using general procedure G, using methyl (4-vinylphenyl)acetate **4.21c** (33.0 mg, 0.2 mmol) as the starting material and obtained as a white solid (66.9 mg, 93% NMR yield, 88% isolated yield, 16:1 dr). **mp**: 102-109 °C. **Rf**: 0.12 (50% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.26 (dt, *J* = 8.4, 2.7 Hz, 2 H, Ar), 6.94 (dt, *J* = 8.4, 2.3 Hz, 2 H, Ar), 2.28 (s, 3 H, C**H**$_3$), 2.12 (dd, *J* = 6.8, 5.2 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.51 (dd, *J* = 4.8, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.02 (dd, *J* = 7.0, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.97 (s, 6 H, 2×C_{pin}**H**$_3$), 0.90 (s, 6 H, 2×C_{pin}**H**$_3$), 0.07 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 169.5 (**C**=O), 148.8 (**C**qO, Ar), 139.0 (**C**q, Ar), 129.6 (2×**C**H, Ar), 120.8 (2×**C**H, Ar), 82.7 (2×**C**qO), 24.9 (2×**C**$_{pin}$H$_3$), 24.50 (Ar**C**$_{cyclopropyl}$H), 24.46 (2×**C**$_{pin}$H$_3$), 21.1 (CO**C**H$_3$), 12.7 (**C**$_{cyclopropyl}$H$_2$), 3.6 (**C**qBSi), –2.3 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.4. **FTIR** (cm^{-1}) (neat): 2977, 1769 (C=O), 1509, 1361, 1301, 1245, 1165, 1146, 1117, 880, 849. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{20}H_{31}{}^{11}BO_4Si$ $[M+H]^+$: 375.2157; found 375.2175.

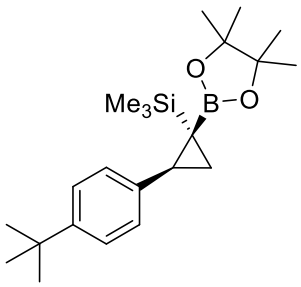
Trimethyl((1*S,2*R**)-2-(4-(methylthio)phenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)silane (4.22d)**



Cyclopropane **4.22d** was synthesized using general procedure G, using methyl(4-vinylphenyl)sulfane[202] **4.21d** (30.0 mg, 0.2 mmol) as the starting material and obtained as a white solid (69.9 mg, 91% NMR yield, 91% isolated yield, 13:1 dr). **mp**: 38-45 °C. **Rf**: 0.27 (50% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.23-7.15 (m, 4 H, Ar), 2.45 (s, 3 H, C**H$_3$**), 2.10 (dd, *J* = 6.9, 5.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.50 (dd, *J* = 4.7, 3.8 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.02 (dd, *J* = 7.0, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.98 (s, 6 H, 2×C_{pin}**H$_3$**), 0.91 (s, 6 H, 2×C_{pin}**H$_3$**), 0.08 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 139.0 (**C**q, Ar), 135.0 (**C**q, Ar), 129.2 (2×**C**H, Ar), 127.2 (2×**C**H, Ar), 82.7 (2×**C**qO), 24.9 (2×**C**$_{pin}$H$_3$), 24.6 (Ar**C**$_{cyclopropyl}$H), 24.5 (2×**C**$_{pin}$H$_3$), 16.9 (S**C**H$_3$), 12.6 (**C**$_{cyclopropyl}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$)

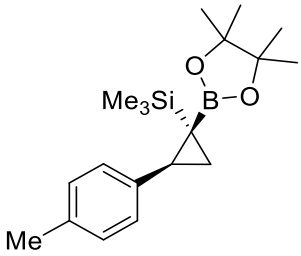
δ ppm 33.1. **FTIR** (cm^{-1}) (neat): 2977, 1495, 1360, 1301, 1245, 1146, 1117, 879, 837. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{31}{}^{11}BO_2SSi$ $[M+H]^+$: 363.1979, found 363.1975.

((1*S,2*R**)-2-(4-(*tert*-Butyl)phenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22e)**



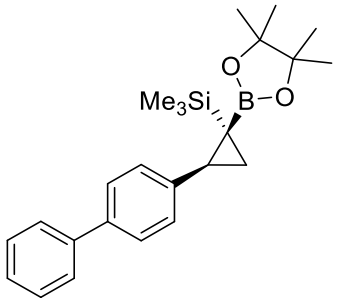
Cyclopropane **4.22e** was synthesized using general procedure G, using 4-*t*-butylstyrene **4.21e** (34.7 mg, 0.2 mmol) as the starting material and obtained as a white solid (66.5 mg, 86% NMR yield, 82% isolated yield, 14:1 dr). **mp**: 61-79 °C. **Rf**: 0.08 (10% CH_2Cl_2/hexanes). *Major diastereomer*. **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.26 (dt, *J* = 8.4, 2.0 Hz, 2 H, Ar), 7.18 (dt, *J* = 8.3, 2.1 Hz, 2 H, Ar), 2.13 (dd, *J* = 6.9, 5.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.52 (dd, *J* = 4.9, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.29 (s, 9 H, 3×$C_{t\text{-}Bu}$**H**$_3$), 1.00 (dd, *J* = 7.0, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.94 (s, 6 H, 2×C_{pin}**H**$_3$), 0.86 (s, 6 H, 2×C_{pin}**H**$_3$), 0.08 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 148.5 (**C**q, Ar), 138.3 (**C**q, Ar), 128.2 (2×**C**H, Ar), 124.7 (2×**C**H, Ar), 82.6 (2×**C**qO), 34.3 (**C**q(CH$_3$)$_3$), 31.4 (3×**C**$_{t\text{-}Bu}$H$_3$), 24.8 (2×**C**$_{pin}$H$_3$), 24.5 (Ar**C**$_{cyclopropyl}$H), 24.4 (2×**C**$_{pin}$H$_3$), 12.3 (**C**$_{cyclopropyl}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.1. **FTIR** (cm^{-1}) (neat): 2960, 1359, 1300, 1245, 1146, 1117, 836, 759. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{22}H_{37}{}^{11}BO_2Si$ $[M+H]^+$: 373.2728; found 373.2739.

Trimethyl((1*S,2*R**)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(p-tolyl)cyclopropyl)silane (4.22f)**



Cyclopropane **4.22f** was synthesized using general procedure G, using 4-methylstyrene **4.21f** (28.3 mg, 0.2 mmol) as the starting material and obtained as a white solid (75.6 mg, 98% NMR yield, 96% isolated yield, 10:1 dr). **mp**: 36-40 °C. **Rf**: 0.14 (15% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.14 (d, *J* = 8.0 Hz, 2 H, Ar), 7.03 (d, *J* = 7.9 Hz, 2 H, Ar), 2.30 (s, 3 H, C**H$_3$**), 2.10 (dd, *J* = 6.7, 5.1 Hz, 1 H, ArC$_{cyclopropyl}$**H**), 1.49 (dd, *J* = 4.9, 3.6 Hz, 1 H, 1×C$_{cyclopropyl}$**H$_2$**), 1.00 (dd, *J* = 7.1, 3.5 Hz, 1 H, 1×C$_{cyclopropyl}$**H$_2$**), 0.97 (s, 6 H, 2×C$_{pin}$**H$_3$**), 0.90 (s, 6 H, 2×C$_{pin}$**H$_3$**), 0.08 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.3 (**C**q, Ar), 135.1 (**C**q, Ar), 128.44 (2×**C**H, Ar), 128.42 (2×**C**H, Ar), 82.5 (2×**C**qO), 24.9 (2×**C**$_{pin}$H$_3$), 24.7 (Ar**C**$_{cyclopropyl}$H), 24.5 (2×**C**$_{pin}$H$_3$), 21.0 (Ar**C**H$_3$), 12.6 (**C**$_{cyclopropyl}$H$_2$), 3.7 (**C**qBSi), –2.3 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.1. **FTIR** (cm^{-1}) (neat): 2925, 1360, 1301, 1246, 1145, 1117, 838, 739. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{31}{}^{11}BO_2Si$ $[M+H]^+$: 331.2259; found 331.2248.

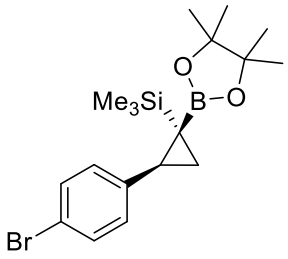
((1*S,2*R**)-2-([1,1'-Biphenyl]-4-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclopropyl)trimethylsilane (4.22g)**



Cyclopropane **4.22g** was synthesized using general procedure G, using methyl 4-vinylbiphenyl **4.21g** (36.0 mg, 0.2 mmol) as the starting material and obtained as a white solid (63.2 mg, 94% NMR yield, 81% isolated yield, 13:1 dr). **mp**: 110-117 °C. **Rf**: 0.30 (30% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.58-7.56 (m, 2 H, Ar), 7.49-7.43 (m, 4 H, Ar), 7.36-7.33 (m, 3 H, Ar), 2.19 (dd, *J* = 6.7, 5.2 Hz, 1 H, ArC$_{cyclopropyl}$**H**), 1.58 (dd, *J* = 4.8, 3.8 Hz, 1 H, 1×C$_{cyclopropyl}$**H$_2$**), 1.07 (dd, *J* = 7.0, 3.6 Hz, 1 H, 1×C$_{cyclopropyl}$**H$_2$**), 0.97 (s, 6 H, 2×C$_{pin}$**H$_3$**), 0.91 (s, 6 H, 2×C$_{pin}$**H$_3$**), 0.11 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 141.4 (**C**q, Ar), 140.7 (**C**q, Ar), 138.7 (**C**q, Ar), 129.0 (2×**C**H, Ar), 128.7 (2×**C**H, Ar), 127.0 (2×**C**H, Ar), 126.9 (**C**H, Ar), 126.6 (2×**C**H, Ar), 82.7 (2×**C**qO), 24.9 (2×**C**$_{pin}$H$_3$), 24.8 (Ar**C**$_{cyclopropyl}$H), 24.5 (2×**C**$_{pin}$H$_3$), 12.7 (**C**$_{cyclopropyl}$H$_2$), 4.1 (**C**qBSi), –2.3 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$)

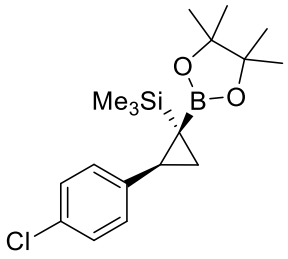
δ ppm 32.6. **FTIR** (cm^{-1}) (neat): 2974, 1485, 1359, 1334, 1298, 1247, 1220, 1147, 1116, 958, 839, 749, 696. **HRMS** (ESI, Pos) calculated for $C_{24}H_{33}{}^{11}BO_2Si$ $[M+H]^+$: 393.2415 m/z, found 393.2422 m/z.

((1*S,2*R**)-2-(4-Bromophenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) trimethylsilane (4.22h)**



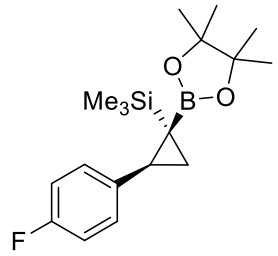
Cyclopropane **4.22h** was synthesized using general procedure G, using 4-bromostyrene **4.21h** (40.1 mg, 0.2 mmol) as the starting material and obtained as a white solid (50.2 mg, 75% NMR yield, 58% isolated yield, 14:1 dr). **mp**: 30-31 °C. **Rf**: 0.25 (15% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.35 (dt, *J* = 8.4, 2.2 Hz, 2 H, Ar), 7.13 (dt, *J* = 8.3, 2.3 Hz, 2 H, Ar), 2.07 (dd, *J* = 6.7, 5.3 Hz, 1 H, $ArC_{cyclopropyl}\mathbf{H}$), 1.48 (dd, *J* = 4.8, 3.8 Hz, 1 H, $1\times C_{cyclopropyl}\mathbf{H}_2$), 1.03 (dd, *J* = 7.0, 3.7 Hz, 1 H, $1\times C_{cyclopropyl}\mathbf{H}_2$), 0.98 (s, 6 H, $2\times C_{pin}\mathbf{H_3}$), 0.91 (s, 6 H, $2\times C_{pin}\mathbf{H_3}$), 0.07 (s, 9 H, $Si(C\mathbf{H}_3)_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 140.6 (**C**q, Ar), 130.8 (2×**C**H, Ar), 130.4 (2×**C**H, Ar), 119.3 (**C**q, Ar-Br), 82.8 (2×**C**qO), 24.9 ($2\times\mathbf{C}_{pin}H_3$), 24.54 ($Ar\mathbf{C}_{cyclopropyl}H$), 24.46 ($2\times\mathbf{C}_{pin}H_3$), 12.7 ($\mathbf{C}_{cyclopropyl}H_2$), –2.4 ($Si(\mathbf{C}H_3)_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.8. **FTIR** (cm^{-1}) (neat): 2978, 1489, 1361, 1303, 1146, 1117, 852, 837. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{18}H_{28}{}^{11}BBrO_2Si$ $[M+H]^+$: 395.1208; found 395.1222.

((1*S,2*R**)-2-(4-Chlorophenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) trimethylsilane (4.22i)**



Cyclopropane **4.22i** was synthesized using general procedure G, using 4-chlorostyrene **4.21i** (27.7 mg, 0.2 mmol) as the starting material and obtained as a white solid (55.4 mg, 91% NMR yield, 79% isolated yield, 15:1 dr). **mp**: 56-59 °C. **Rf**: 0.07 (15% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.23-7.17 (m, 4 H, Ar), 2.09 (dd, *J* = 6.9, 5.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.49 (dd, *J* = 4.9, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.03 (dd, *J* = 7.0, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.98 (s, 6 H, 2×C_{pin}**H**$_3$), 0.91 (s, 6 H, 2×C_{pin}**H**$_3$), 0.07 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 140.0 (**C**q, Ar), 131.3 (**C**q, Ar-Cl), 130.0 (2×**C**H, Ar), 127.8 (2×**C**H, Ar), 82.7 (2×**C**qO), 24.9 (2×**C**$_{pin}$H$_3$), 24.48 (Ar**C**$_{cyclopropyl}$H**)**, 24.46 (2×**C**$_{pin}$H$_3$), 12.7 (**C**$_{cyclopropyl}$H$_2$), –2.4 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.5. **FTIR** (cm^{-1}) (neat): 2924, 1494, 1360, 1303, 1146, 1116, 879, 836. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{18}H_{28}{}^{11}BClO_2Si$ $[M+H]^+$: 351.1713; found 351.1709.

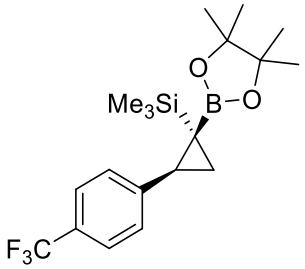
((1*S,2*R**)-2-(4-Fluorophenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) trimethylsilane (4.22j)**



Cyclopropane **4.22j** was synthesized using general procedure G, using 4-fluorostyrene **4.21j** (25.4 mg, 0.2 mmol) as the starting material and obtained as a white solid (41.7 mg, 81% NMR yield, 60% isolated yield, 13:1 dr). **mp**: 64-67 °C. **Rf**: 0.18 (15% dichloromethane /hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.24-7.20 (m, 2 H, Ar), 6.94-6.90 (m, 2 H, Ar), 2.11 (dd, *J* = 6.9, 5.4 Hz, 1 H, Ar$C_{cyclopropyl}$**H)**, 1.48 (dd, *J* = 4.9, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.02 (dd, *J* = 7.0, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.98 (s, 6 H, 2×C_{pin}**H**$_3$), 0.89 (s, 6 H, 2×C_{pin}**H**$_3$), 0.08 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 161.3 (d, *J* = 245 Hz, **C**-F), 137.1 (d, *J* = 3.1 Hz, **C**q, Ar), 130.2 (d, *J* = 7.8 Hz, 2×**C**H, Ar), 114.4 (d, *J* = 21.4 Hz, 2×**C**H, Ar), 82.7 (2×**C**qO), 24.9 (2×**C**$_{pin}$H$_3$), 24.4 (2×**C**$_{pin}$H$_3$), 24.3 (Ar**C**$_{cyclopropyl}$H**)**, 12.6 (**C**$_{cyclopropyl}$H$_2$), 3.5 (**C**qBSi), –2.4 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.9. **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm –117.9

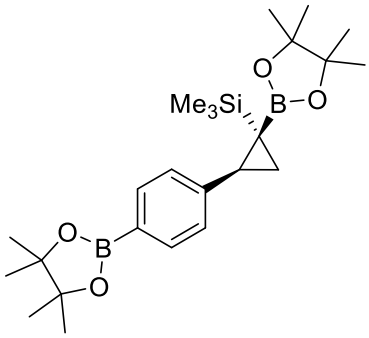
(s, 1 F). **FTIR** (cm^{-1}) (neat): 2978, 1511, 1361, 1332, 1146, 1117, 837, 756. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{18}H_{29}{}^{11}BFO_2Si$ $[M+H]^+$: 335.2008; found 335.2022.

Trimethyl((1*S,2*R**)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-(trifluoromethyl) phenyl)cyclopropyl)silane (4.22k)**



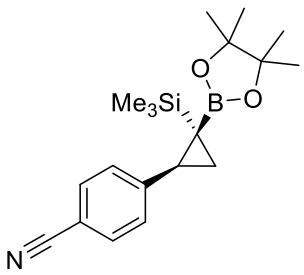
Cyclopropane **4.22k** was synthesized using general procedure G, using 4-(trifluoromethyl)styrene **4.21k** (35.5 mg, 0.2 mmol) as the starting material and obtained as a white solid (79.3 mg, 41% NMR yield, 41% isolated yield, 18:1 dr). **mp**: 49-54 °C. **Rf**: 0.12 (15% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.49 (d, *J* = 8.2 Hz, 2 H, Ar), 7.35 (d, *J* = 8.3 Hz, 2 H, Ar), 2.17 (dd, *J* = 6.6, 5.3 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.57 (dd, *J* = 4.9, 3.9 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.09 (dd, *J* = 6.9, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.95 (s, 6 H, 2×C_{pin}**H**$_3$), 0.89 (s, 6 H, 2×C_{pin}**H**$_3$), 0.09 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 145.9 (**C**q-cyclopropyl, Ar), 128.8 (2×**C**H, Ar), 127.9 (dd, *J* = 298, 330 Hz, **C**F_3), 124.7 (q, *J* = 3.5 Hz, 2×**C**HAr-CF_3), 82.8 (2×**C**qO), 24.9 (Ar**C**$_{cyclopropyl}$H), 24.8 (2×**C**$_{pin}$H$_3$), 24.4 (2×**C**$_{pin}$H$_3$), 12.8 (**C**$_{cyclopropyl}$H$_2$), –2.4 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.1. **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm –62.3 (s, 3 F). **FTIR** (cm^{-1}) (neat): 2978, 1361, 1325, 1248, 1165, 1144, 1069, 844. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{28}{}^{11}BF_3O_2Si$ $[M+H]^+$: 385.1977; found 385.1984.

Trimethyl((1*S,2*R**)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan–2-yl)phenyl)cyclopropyl)silane (4.22l)**



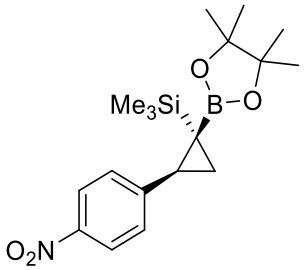
Cyclopropane **4.22l** was synthesized using general procedure G, using 4,4,5,5-tetramethyl–2-(4-vinylphenyl)-1,3,2-dioxaborolane[203] **4.21l** (46.0 mg, 0.2 mmol) as the starting material and obtained as a white solid (40.6 mg, 83% NMR yield, 46% isolated yield, 9:1 dr). **mp**: 76-78 °C. **Rf**: 0.27 (70% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.67 (d, *J* = 8.0 Hz, 2 H, Ar), 7.24 (d, 2H, *J* = 7.9 Hz, 2 H, Ar), 2.12 (d, *J* = 6.8, 5.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.54 (dd, *J* = 4.9, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H_2**), 1.35 (s, 12 H, 4×C_{pin}**H_3**), 1.05 (dd, *J* = 7.0, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H_2**), 0.97 (s, 6 H, 2×C_{pin}**H_3**), 0.92 (s, 6 H, 2×C_{pin}**H_3**), 0.08 (s, 9 H, Si(C**H_3**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 145.1 (**C**$q_{cyclopropyl}$, Ar), 134.4 (2×CH, Ar), 127.7 (2×CH, Ar), 83.5 (2×**C**qO), 82.7 (2×**C**qO), 25.4 (Ar**C**$_{cyclopropyl}$H**)**, 24.93 (2×**C**$_{pin}H_3$), 24.87 (2×**C**$_{pin}H_3$), 24.78 (2×**C**$_{pin}H_3$), 24.5 (2×**C**$_{pin}H_3$), 13.1 (**C**$_{cyclopropyl}H_2$), –2.4 (Si(**C**H_3)$_3$). Carbons attached to the boron were not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 31.1. **FTIR** (cm^{-1}) (neat): 2979, 2361, 2190, 2165, 2146, 1610, 1360, 1246, 1146, 1090, 840, 667. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{24}H_{40}{}^{11}B_2O_4Si$ $[M+H]^+$: 443.2955; found 443.2949.

4-((1*R,2*S**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl) benzonitrile (4.22m)**



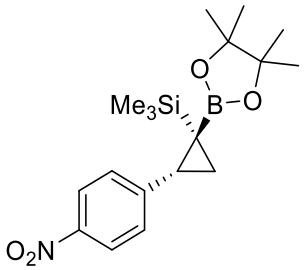
Cyclopropane **4.22m** was synthesized using general procedure G, using 4-cyanostyrene **4.21m** (25.8 mg, 0.2 mmol) as the starting material and obtained as a white solid (15.6 mg, 23% NMR yield, 23% isolated yield, 10:1 dr). **mp**: 79-85 °C. **Rf**: 0.44 (60% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.52 (d, *J* = 8.4 Hz, 2 H, Ar), 7.33 (d, *J* = 8.2 Hz, 2 H, Ar), 2.14 (dd, *J* = 6.5, 5.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.56 (dd, *J* = 4.9, 3.9 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.10 (dd, *J* = 6.8, 3.8 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.96 (s, 6 H, 2×C_{pin}**H**$_3$), 0.91 (s, 6 H, 2×C_{pin}**H**$_3$), 0.08 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 147.7 (**C**q, Ar), 131.6 (2×**C**H, Ar), 129.2 (2×**C**H, Ar), 119.3 (**C**N), 109.2 (**C**q, Ar), 82.9 (2×**C**qO), 25.3 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}$H$_3$), 24.6 (2×**C**$_{pin}$H$_3$), 13.2 (**C**$_{cyclopropyl}$H$_2$), 5.5 (**C**qBSi), –2.5 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 31.7. **FTIR** (cm^{-1}) (neat): 2978, 2227, 1608, 1358, 1303, 1246, 1166, 1143, 1116, 1070, 960, 877, 836, 755, 689, 558. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{28}{}^{11}BNO_2Si$ $[M+H]^+$: 342.2059; found 342.2055.

Trimethyl((1*S,2*R**)-2-(4-nitrophenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclopropyl)silane (4.22n)**



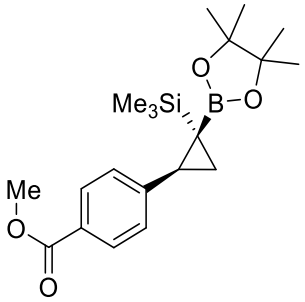
Cyclopropane **4.22n** was synthesized using general procedure G, using 4-nitrostyrene **4.21n** (32.5 mg, 0.2 mmol) as the starting material and obtained as an orange solid (36.9 mg, 36% NMR yield, 34% isolated yield). **mp**: 56-66 °C. **Rf**: 0.31 (40% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 8.10 (dt, *J* = 8.9, 2.2 Hz, 2 H, Ar), 7.37 (dt, *J* = 8.7, 2.2 Hz, 2 H, Ar), 2.18 (dd, *J* = 6.6, 5.2, Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.61 (dd, *J* = 4.8, 4.0 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.15 (dd, *J* = 6.9, 3.8 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.96 (s, 6 H, 2×C_{pin}**H**$_3$), 0.92 (s, 6 H, 2×C_{pin}**H**$_3$), 0.09 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 150.1 (**C**q, Ar-NO_2), 146.0 (**C**q, Ar), 129.1 (2×**C**H, Ar), 123.1 (2×**C**H, Ar), 83.0 (2×**C**qO), 25.2 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}$H$_3$), 24.6 (2×**C**$_{pin}$H$_3$), 13.7 (**C**$_{cyclopropyl}$H$_2$), 6.1 (**C**qBSi), –2.5 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.9. **FTIR** (cm^{-1}) (neat): 2978, 1599, 1519, 1344, 1247, 1145, 1116, 848. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{18}H_{28}{}^{11}BNO_4Si$ $[M+H]^+$: 362.1953; found 362.1959.

Trimethyl((1*R,2*R**)-2-(4-nitrophenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)silane (4.22n')**



Cyclopropane **4.22n'** was synthesized using general procedure G, using 4-nitrostyrene **4.21n** (32.5 mg, 0.2 mmol) as the starting material and obtained as an orange solid (7.9 mg, 14% NMR yield, 11% isolated yield). **Rf**: 0.35 (40% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 8.14-8.11 (m, 2 H, Ar), 7.45 (dt, 2 H, *J* = 8.3, 2.5 Hz, Ar), 2.54 (dd, *J* = 7.2, 5.8 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.38 (dd, *J* = 7.3, 3.3 Hz, 1 H 1×$C_{cyclopropyl}$**H**$_2$), 1.24-1.22 (m, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.26 (s, 6 H, 2×C_{pin}**H**$_3$), 1.25 (s, 6 H, 2×C_{pin}**H**$_3$), −0.25 (s, 9H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 149.2 (**C**q, Ar-NO_2), 146.4 (**C**q, Ar), 130.9 (2×**C**H, Ar), 123.0 (2×**C**H, Ar), 83.0 (2×**C**qO), 27.2 (Ar**C**$_{cyclopropyl}$H), 24.8 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 12.7 (**C**$_{cyclopropyl}$H$_2$), –0.8 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation.

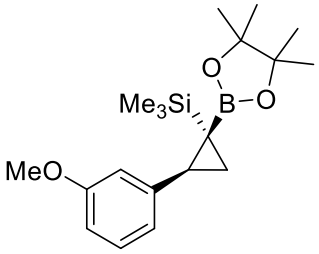
Methyl 4-((1*R,2*S**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2(trimethylsilyl)cyclopropyl)benzoate (4.22o)**



Cyclopropane **4.22o** was synthesized using general procedure G, using methyl 4-vinylbenzoate **4.21o** (32.4 mg, 0.2 mmol) as the starting material and obtained as a white solid (32.9 mg, 47% NMR yield, 44% isolated yield, 12:1 dr). **mp**: 79-89 °C. **Rf**: 0.20 (10% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.91 (dt, *J* = 8.3, 2.8 Hz, 2 H, Ar), 7.30 (dt, *J* = 8.3, 1.9 Hz, 2 H, Ar), 3.91 (s, 3 H, COC**H**$_3$), 2.15 (dd, *J* = 6.7, 5.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.58

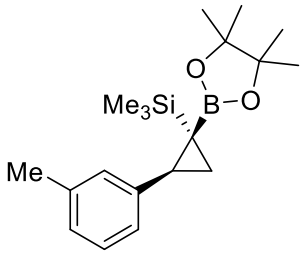
(dd, J = 4.9, 3.8 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.08 (dd, J = 6.9, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.95 (s, 6 H, 2×C_{pin}**H**$_3$), 0.91 (s, 6 H, 2×C_{pin}**H**$_3$), 0.08 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 167.3 (**C**=O), 147.4 (**C**q, Ar), 129.2 (**C**q, Ar), 128.4 (2×**C**H, Ar), 127.4 (2×**C**H, Ar), 82.8 (2×**C**qO), 51.9 (O**C**H$_3$), 25.2 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 13.2 (**C**$_{cyclopropyl}$H$_2$), 5.0 (**C**qBSi), –2.4 Si(**C**H$_3$)$_3$. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.0. **FTIR** (cm^{-1}) (neat): 2978, 1724, 1610, 1435, 1360, 1246, 1146, 1109, 849, 700. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{20}H_{31}{}^{11}BO_4Si$ $[M+H]^+$: 375.2157; found 375.2148.

((1*S,2*R**)-2-(3-Methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22p)**



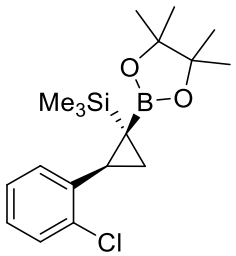
Cyclopropane **4.22p** was synthesized using general procedure G, using 3-methoxystyrene **4.21p** (75.4 mg, 0.2 mmol) as the starting material and obtained as a white solid (43.6 mg, 95% NMR yield, 62% isolated yield, 11:1 dr). **mp**: 38-44 °C. **Rf**: 0.34 (40% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.14 (t, J = 7.9 Hz, 1 H, Ar), 6.87 (dt, J = 7.6, 1.6 Hz, 1 H, Ar), 6.81 (m, J = 1.9 Hz, 1 H, Ar), 6.69 (dd, J = 7.9, 2.4 Hz, 1 H, Ar), 3.81 (s, 3 H, OC**H**$_3$), 2.12 (dd, J = 6.9, 5.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.51 (dd, J = 4.9, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.02 (dd, J = 7.0, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.98 (s, 6H, 2×C_{pin}**H**$_3$), 0.92 (s, 6H, 2×C_{pin}**H**$_3$), 0.08 (s, 9H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 159.2 (**C**q, Ar-OMe), 143.1 (**C**q, Ar), 128.8 (**C**H, Ar), 121.1 (**C**H, Ar), 114.2 (**C**H, Ar), 111.2 (**C**H, Ar), 82.6 (2×**C**qO), 55.1 (O**C**H$_3$), 25.1 (Ar**C**$_{cyclopropyl}$H**)**, 24.9 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 12.7 (**C**$_{cyclopropyl}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.2. **FTIR** (cm^{-1}) (neat): 2926, 1602, 1465, 1361, 1248, 1146, 968, 849, 692. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{31}{}^{11}BO_3Si$ $[M+H]^+$: 347.2208, found 347.2220.

Trimethyl((1*S,2*R**)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(*m*-tolyl)cyclopropyl) silane (4.22q)**



Cyclopropane **4.22q** was synthesized using general procedure G, using 3-methylstyrene **4.21q** (34.6 mg, 0.2 mmol) as the starting material and obtained as a colorless oil (54.8 mg, 94% NMR yield, 76% isolated yield, 14:1 dr). **Rf**: 0.14 (15% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.11 (t, *J* = 7.7 Hz, 1 H, Ar), 7.05-7.07 (m, 2H, Ar), 6.94 (d, *J* = 7.5 Hz, 1 H, Ar), 2.31 (s, 3 H, C**H$_3$**), 2.11 (dd, *J* = 7.9, 5.1 Hz, 1 H, ArC$_{cyclopropyl}$**H**), 1.51 (dd, *J* = 4.9, 3.6 Hz, 1 H, 1×C$_{cyclopropyl}$**H$_2$**), 1.00 (dd, *J* = 7.0, 3.5 Hz, 1 H, 1×C$_{cyclopropyl}$**H$_2$**), 0.97 (s, 6 H, 2×C$_{pin}$**H$_3$**), 0.91 (s, 6 H, 2×C$_{pin}$**H$_3$**), 0.08 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 141.3 (**C**q, Ar), 137.1 (**C**q, Ar-Me), 129.1 (**C**H, Ar), 127.7 (**C**H, Ar), 126.4 (**C**H, Ar), 125.7 (**C**H, Ar), 82.6 (2×**C**qO), 25.0 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 21.4 (**C**H$_3$), 12.6 (**C**$_{cyclopropyl}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.4. **FTIR** (cm^{-1}) (neat): 2977, 1360, 1331, 1300, 1145, 956, 836, 695. **HRMS** (ESI, Pos) *m/z:* calcd for $(C_{19}H_{31}{}^{11}BO_2Si)^+$ 331.2259; found 331.2254.

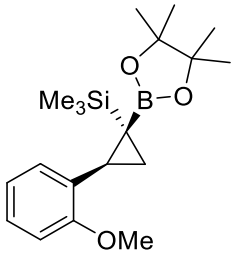
((1*S,2*R**)-2-(3-Chlorophenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) (4.22r)**



Cyclopropane **4.22r** was synthesized using general procedure G, using 3-chlorostyrene **4.21r** (30.8 mg, 0.2 mmol) as the starting material and obtained as a white solid (42.6 mg, 55% NMR

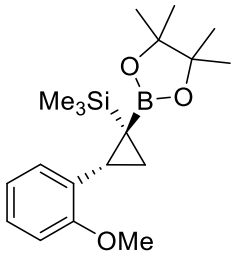
yield, 55% isolated yield, 14:1 dr). **mp**: 71-75 °C. **Rf**: 0.29 (15% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.21 (m, 1 H, Ar), 7.17-7.14 (m, 2 H, Ar), 7.13-7.10 (m, 1 H, Ar), 2.10 (dd, *J* = 7.0, 5.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.50 (dd, *J* = 4.9, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.05 (dd, *J* = 7.0, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.00 (s, 6 H, 2×C_{pin}**H**$_3$), 0.94 (s, 6 H, 2×C_{pin}**H**$_3$), 0.08 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 143.8 (**C**q, Ar), 133.6 (**C**q, Ar), 129.0 (**C**H, Ar), 128.2 (**C**H, Ar), 127.1 (**C**H, Ar), 125.8 (**C**H, Ar), 82.8 (2×**C**qO), 24.9 (2×**C**$_{pin}$H$_3$), 24.8 (Ar**C**$_{cyclopropyl}$H**)**, 24.6 (2×**C**$_{pin}$H$_3$), 12.9 (**C**$_{cyclopropyl}$H$_2$), –2.4 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.3. **FTIR** (cm^{-1}) (neat): 2978, 1596, 1360, 1304, 1247, 1145, 947, 850, 692. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{18}H_{28}{}^{11}BClO_2Si[M+H]^+$: 351.1713; found 351.1716.

((1*S,2*R**)-2-(2-Methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22s)**



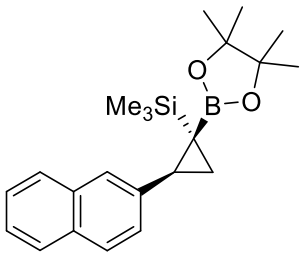
Cyclopropane **4.22s** was synthesized using general procedure G, using 2-vinylanisole **4.21s** (30.7 mg, 0.2 mmol) as the starting material and obtained as a white solid (51.6 mg, 65% NMR yield, 65% isolated yield). **mp**: 55-57 °C. **Rf**: 0.09 (20% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.14-7.11 (m, 2 H, Ar), 6.82 (td, *J* = 7.4, 0.7 Hz, 1 H, Ar) 6.79 (dd, *J* = 8.4, 0.7 Hz, 2 H, Ar), 3.85 (s, 3 H, OC**H**$_3$), 2.16 (dd, *J* = 6.4, 5.5 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.49 (dd, *J* = 5.1, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.97 (dd, *J* = 6.9, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.91 (s, 6 H, 2×C_{pin}**H**$_3$), 0.81 (s, 6 H, 2×C_{pin}**H**$_3$), 0.09 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 159.6 (**C**q, Ar-OMe), 130.1 (**C**q, Ar), 128.2 (**C**H, Ar), 126.8 (**C**H, Ar), 119.7 (**C**H, Ar), 109.7 (**C**H, Ar), 82.2 (2×**C**qO), 55.1 (**C**H$_3$), 24.7 (2×**C**$_{pin}$H$_3$), 24.4 (2×**C**$_{pin}$H$_3$), 20.4 (Ar**C**$_{cyclopropyl}$H**)**, 11.3 (**C**$_{cyclopropyl}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 31.8. **FTIR** (cm^{-1}) (neat): 2979, 1370, 1331, 1302, 1265, 1247, 1139, 846, 750. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{31}{}^{11}BO_3Si$ $[M+H]^+$: 347.2208; found 347.2225.

((1*S,2*S**)-2-(2-Methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22s')**



Cyclopropane **4.22s'** was synthesized using general procedure G, using 2-vinylanisole **4.21s** (30.7 mg, 0.2 mmol) as the starting material and obtained as a yellow oil (17.2 mg, 22% NMR yield, 22% isolated yield). **Rf**: 0.05 (20% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.19 (td, *J* = 8.0, 1.7, Hz, 1 H Ar), 7.11 (d, *J* = 7.4 Hz, 1 H, Ar), 6.84 (td, *J* = 7.4, 0.7 Hz, 1 H, Ar), 6.79 (d, *J* = 8.1 Hz, 1 H, Ar), 3.84 (s, 3 H, OC**H$_3$**), 2.36 (t, *J* = 6.4 Hz, 1 H, ArC$_{cyclopropyl}$**H**), 1.28-1.30 (m, 1 H, 1×C$_{cyclopropyl}$**H$_2$**), 1.27 (s, 6 H, 2×C$_{pin}$**H$_3$**), 1.26 (s, 6 H, 2×C$_{pin}$**H$_3$**), 1.23 (dd, *J* = 5.8, 3.2 Hz, 1 H 1×C$_{cyclopropyl}$**H$_2$**), −0.29 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 159.5 (**C**q, Ar-OMe), 129.3 (**C**q, Ar), 129.1 (**C**H, Ar), 127.2 (**C**H, Ar), 119.4 (**C**H, Ar), 109.2 (**C**H, Ar), 82.5 (2×**C**qO), 54.8 (**C**H$_3$), 24.7 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 23.5 (Ar**C**$_{cyclopropyl}$H), 11.7 (**C**$_{cyclopropyl}$H$_2$), –0.9 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.2. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{31}{}^{11}BO_3Si$ $[M+H]^+$: 347.2208; found 347.2220.

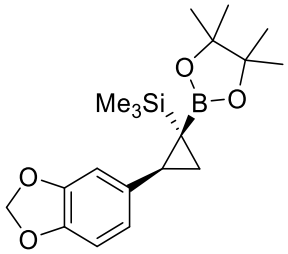
Trimethyl((1*S,2*R**)-2-(naphthalen-2-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)silane (4.22t)**



Cyclopropane **4.22t** was synthesized using general procedure G, using 2-vinylnaphthalene **4.21t** (31.2 mg, 0.2 mmol) as the starting material and obtained as a white solid (60.6 mg, 82% NMR yield, 82% isolated yield, 13:1 dr). **mp**: 130-135 °C. **Rf**: 0.35 (30% CH_2Cl_2/hexanes). *Major*

diastereomer. **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.78 (dd, *J* = 8.2, 0.9 Hz, 2 H, Ar), 7.73 (d, *J* = 8.5 Hz, 1 H, Ar), 7.68 (s, 1 H, Ar), 7.46-7.43 (m, 2 H, Ar), 7.41 (td, *J* = 8.3, 1.4 Hz, 2 H, Ar), 2.31 (dd, *J* = 6.4, 5.3 Hz, 1 H, $ArC_{cyclopropyl}\mathbf{H}$), 1.70 (dd, *J* = 4.9, 3.7 Hz, 1 H, $1\times C_{cyclopropyl}\mathbf{H}_2$), 1.13 (dd, *J* = 7.0, 3.6 Hz, 1 H, $1\times C_{cyclopropyl}\mathbf{H}_2$), 0.87 (s, 6 H, $2\times C_{pin}\mathbf{H_3}$), 0.79 (s, 6 H, $2\times C_{pin}\mathbf{H_3}$), 0.14 (s, 9 H, $Si(C\mathbf{H_3})_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 139.2 (**C**q, Ar), 133.4 (**C**q, Ar), 132.1 (**C**q, Ar), 128.0 (**C**H, Ar), 127.5 (**C**H, Ar), 127.5 (**C**H, Ar), 127.2 (**C**H, Ar), 125.8 (**C**H, Ar), 125.7 (**C**H, Ar), 124.9 (**C**H, Ar), 82.6 ($2\times$**C**qO), 25.4 ($Ar\mathbf{C}_{cyclopropyl}H$), 24.8 ($2\times\mathbf{C}_{pin}H_3$), 24.4 ($2\times\mathbf{C}_{pin}H_3$), 12.8 ($\mathbf{C}_{cyclopropyl}H_2$), –2.3 ($Si(\mathbf{C}H_3)_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.8. **FTIR** (cm^{-1}) (neat): 2977, 1360, 1301, 1246, 1213, 1145, 1113, 957, 849, 755. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{22}H_{31}{}^{11}BO_2Si[M+H]^+$: 367.2259; found 367.2270.

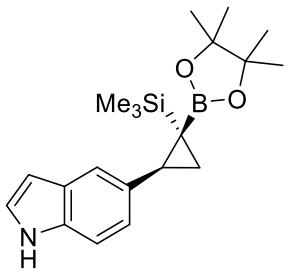
((1*S,2*R**)-2-(Benzo[d][1,3]dioxol-5-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22u)**



Cyclopropane **4.22u** was synthesized using general procedure G, using 5-vinylbenzo[d][1,3]dioxole[204] **4.21u** (29.6 mg, 0.2 mmol) as the starting material and obtained as a white solid (54.1 mg, 76% NMR yield, 75% isolated yield, 12:1 dr). **mp**: 48-52 °C. **Rf**: 0.17 (30% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 6.77-6.73 (m, 2 H, Ar), 6.69 (d, *J* = 7.9 Hz, 1 H, Ar), 5.90 (d, *J* = 2.2 Hz, 1 H, $O_2C\mathbf{H}_2$), 5.88 (d, *J* = 2.2 Hz, 1 H, $O_2C\mathbf{H}_2$), 2.07 (dd, *J* = 6.9, 4.9 Hz, 1 H, $ArC_{cyclopropyl}\mathbf{H}$), 1.42 (dd, *J* = 4.9, 3.6 Hz, 1 H, $1\times C_{cyclopropyl}\mathbf{H}_2$), 1.02 (s, 6 H, $2\times C_{pin}\mathbf{H_3}$), 0.99 (dd, *J* = 7.1, 3.5 Hz, 1 H, $1\times C_{cyclopropyl}\mathbf{H}_2$), 0.94 (s, 6 H, $2\times C_{pin}\mathbf{H_3}$), 0.06 (s, 9 H, $Si(C\mathbf{H_3})_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 147.0 (**C**qO, Ar), 145.5 (**C**qO, Ar), 135.5 (**C**q, Ar), 121.6 (**C**H, Ar), 109.4 (**C**H, Ar), 107.7 (**C**H, Ar), 100.6 ($O_2\mathbf{C}H_2$), 82.6 ($2\times$**C**qO), 24.95 ($2\times\mathbf{C}_{pin}H_3$), 24.91 ($Ar\mathbf{C}_{cyclopropyl}H$), 24.5 ($2\times\mathbf{C}_{pin}H_3$), 12.9 ($\mathbf{C}_{cyclopropyl}H_2$), – 2.3 ($Si(\mathbf{C}H_3)_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.6. **FTIR** (cm^{-1}) (neat): 2977, 1505, 1489, 1359, 1300, 1245, 1212, 1147, 1117, 1040,

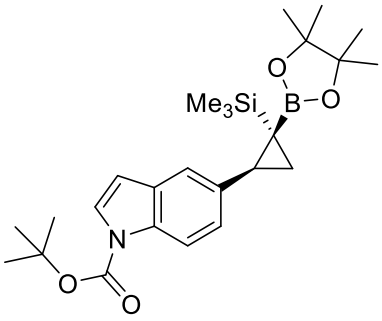
939, 837, 757, 688. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{29}{}^{11}BO_4Si$ $[M+H]^+$: 361.2001; found 361.1999.

5-((1*R,2*S**)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl)-1H-indole (4.22v)**



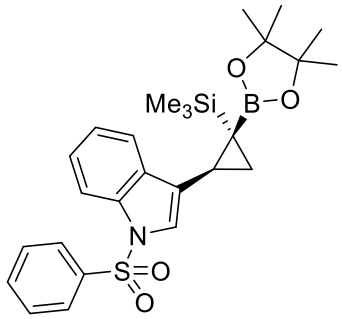
Cyclopropane **4.22v** was synthesized using general procedure G, 5-vinyl-1H-indole[120] **4.21v** (28.6 mg, 0.2 mmol) as the starting material and obtained as a white solid (30.2 mg, 72% NMR yield, 56% isolated yield, 7:1 dr). **mp**: 142-157 °C. **Rf**: 0.22 (20% Et_2O/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 8.04 (s, 1 H, N**H**), 7.51 (s, 1 H, Ar), 7.26 (d, *J* = 8.4 Hz, 1 H, Ar), 7.18-7.14 (m, 2 H, Ar), 6.49-6.47 (t, *J* = 2.2 Hz, 1 H, Ar), 2.28 (dd, *J* = 6.8, 5.2 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.56 (dd, *J* = 4.3, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.06 (dd, *J* = 7.1, 3.4 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.91 (s, 6 H, 2×C_{pin}**H**$_3$), 0.79 (s, 6 H, 2×C_{pin}**H**$_3$), 0.11 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 134.5 (**C**q, Ar), 132.7 (**C**q, Ar), 127.7 (**C**q, Ar), 124.0 (**C**H, Ar), 123.9 (**C**H, Ar), 119.8 (**C**H, Ar), 110.1 (**C**H, Ar), 102.4 (**C**H, Ar), 82.5 (2×**C**qO), 25.3 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}$H$_3$), 24.4 (2×**C**$_{pin}$H$_3$), 12.9 (**C**$_{cyclopropyl}$H$_2$), 3.6 (**C**qBSi), –2.2 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.2. **FTIR** (cm^{-1}) (neat): 3421, 2976, 1477, 1359, 1296, 1245, 1145, 1115, 955, 837, 754, 725. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{20}H_{30}{}^{11}BNO_2Si$ $[M+H]^+$: 356.2212; found 356.2207.

***tert*-Butyl 5-((1*R**,2*S**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl) cyclopropyl)-1H-indole-1-carboxylate (4.22w)**



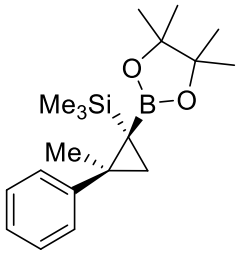
Cyclopropane **4.22w** was synthesized using general procedure G, using *t*-butyl 5-vinyl-1H-indole-1-carboxylate[120] **4.21w** (48.7 mg, 0.2 mmol) as the starting material and obtained as a white solid (68.7 mg, 80% NMR yield, 75% isolated yield, 11:1 dr). *Major diastereomer.* **mp**: 100-102 °C. **Rf**: 0.16 (30% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.97 (d, *J* = 7.4 Hz, 1 H, Ar), 7.55 (d, *J* = 3.0 Hz, 1 H, Ar), 7.42 (s, 1 H, Ar), 7.25 (dd, *J* = 8.5, 1.5 Hz, 1 H, Ar), 6.50 (d, *J* = 3.7 Hz, 1 H, Ar), 2.24 (dd, *J* = 6.9, 5.2 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.69 (s, 9 H, 3×$C_{t\text{-}Bu}$**H$_3$**), 1.57 (dd, *J* = 4.8, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}$**H$_2$**), 1.06 (dd, *J* = 7.1, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H$_2$**), 0.92 (s, 6 H, 2×C_{pin}**H$_3$**), 0.83 (s, 6 H, 2×C_{pin}**H$_3$**), 0.10 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 149.8 (N**C**O), 135.8 (**C**H, Ar), 133.6 (**C**q, Ar), 130.4 (**C**q, Ar), 125.8 (**C**q, Ar), 125.7 (**C**H, Ar), 120.1 (**C**H, Ar), 114.4 (**C**H, Ar), 107.2 (**C**H, Ar), 83.4 (**C**q$_{t\text{-}Bu}$), 82.6 (2×**C**qO), 28.2 (3×**C**$_{t\text{-}Bu}$H$_3$), 25.1 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}$H$_3$), 24.4 (2×**C**$_{pin}$H$_3$), 12.9 (**C**$_{cyclopropyl}$H$_2$), 3.8 (**C**qBSi), –2.3 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.0. **FTIR** (cm^{-1}) (neat): 2978, 1735, 1473, 1367, 1298, 1247, 1224, 1164, 1134, 1086, 1023, 852, 766. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{25}H_{38}{}^{11}BNO_4Si$ $[M+H]^+$: 456.2736; found 456.2740.

1-(Phenylsulfonyl)-3-((1*R,2*S**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl)-1H-indole (4.22x)**



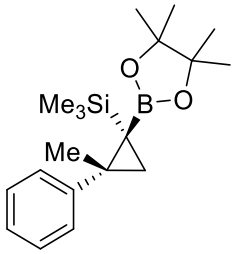
Cyclopropane **4.22x** was synthesized using general procedure G, using 1-(phenylsulfonyl)-3-vinyl-1H-indole[120] **4.21x** (59.2 mg, 0.2 mmol) as the starting material and obtained as a white solid (63.5 mg, 78% NMR yield, 62% isolated yield, 7:1 dr). *Major diastereomer.* **mp**: 116-122 °C. **Rf**: 0.25 (50% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.97 (d, *J* = 8.1 Hz, 1 H, Ar) 7.93-7.92 (m, 2 H, Ar), 7.66 (d, *J* = 7.8 Hz, 1 H, Ar), 7.54 (tt, *J* = 7.5, 1.1 Hz, 1 H, Ar), 7.45 (tt, *J* = 8.0, 1.0 Hz, 2 H, Ar), 7.34 (d, *J* = 1.0 Hz, 1 H, Ar), 7.31 (td, *J* = 7.4, 1.1 Hz, 1 H, Ar), 7.26 (td, *J* = 7.8, 0.8 Hz, 1 H, Ar), 1.97 (tt, *J* = 6.6, 1.1 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.41 (dd, *J* = 4.8, 3.3 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.07 (dd, *J* = 6.9, 3.1 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.77 (s, 6 H, 2×C_{pin}**H**$_3$), 0.66 (s, 6 H, 2×C_{pin}**H**$_3$), 0.12 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.6 (**C**q, Ar), 135.1 (**C**q, Ar), 133.6 (**C**H, Ar), 132.1 (**C**q, Ar), 129.2 (2×**C**H, Ar), 126.8 (2×**C**H, Ar), 124.6 (**C**H, Ar), 123.9 (**C**q, Ar), 123.1 (**C**H, Ar), 122.9 (**C**H, Ar), 120.4 (**C**H, Ar), 113.3 (**C**H, Ar), 82.5 (2×**C**qO), 24.6 (2×**C**$_{pin}$H$_3$), 24.0 (2×**C**$_{pin}$H$_3$), 14.9 (Ar**C**$_{cyclopropyl}$H), 12.2 (**C**$_{cyclopropyl}$H$_2$), 0.8 (**C**qBSi), –2.2 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.8. **FTIR** (cm^{-1}) (neat): 2977, 1447, 1364, 1302, 1245, 1175, 1146, 1128, 877, 852, 744, 685, 636, 596, 570. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{26}H_{35}{}^{11}BNO_4SSi)^+$ 496.2143; found 496.2160.

((1*S,2*R**)-2-Methyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) trimethylsilane (4.22y)**



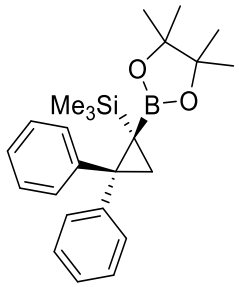
Cyclopropane **4.22y** was synthesized using general procedure G, using α-methylstyrene **4.21y** (23.6 mg, 0.2 mmol) as the starting material and obtained as a colorless oil (13.2 mg, 21% NMR yield, 16% isolated yield). **Rf**: 0.12 (20% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.36 (d, *J* = 7.1 Hz, 2 H, Ph), 7.24 (t, *J* = 7.4 Hz, 2 H, Ph), 7.14 (tt, *J* = 7.4, 1.2 Hz, 1 H, *p*-Ph), 1.69 (d, *J* = 2.8 Hz, 1 H, 1×$C_{cyclopropyl}$**H_2**), 1.50 (s, 3 H, C**H_3**), 0.91 (s, 6 H, 2×C_{pin}**H_3**), 0.89 (d, *J* = 3.3 Hz, 1 H, 1×$C_{cyclopropyl}$**H_2**), 0.72 (s, 6 H, 2×C_{pin}**H_3**), 0.19 (s, 9 H, Si(C**H_3**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 146.7 (**C**q, Ar), 129.1 (2×**C**H, Ar), 127.8 (2×**C**H, Ar), 125.9 (**C**H, Ar), 82.5 (2×**C**qO), 26.3 (CH_3), 25.0 (2×**C**$_{pin}H_3$), 24.6 (2×**C**$_{pin}H_3$), 20.1 (**C**$_{cyclopropyl}H_2$), 0.5 (Si(**C**H_3)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.0. **FTIR** (cm^{-1}) (neat): 2978, 1371, 1328, 1248, 1144, 969, 848, 768, 700. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{31}{}^{11}BO_2Si$ $[M+H]^+$: 331.2259; found 331.2268.

Trimethyl((1*S,2*S**)-2-methyl-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)silane (4.22y')**



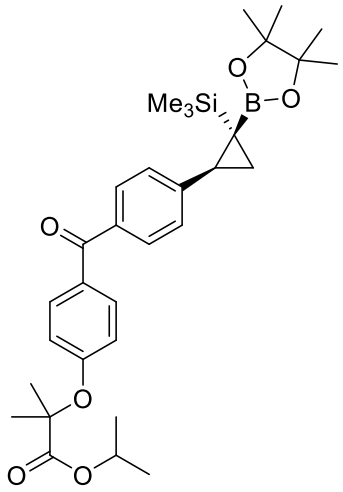
Cyclopropane **4.22y'** was synthesized using general procedure G, using α-methylstyrene **4.21y** (23.6 mg, 0.2 mmol) as the starting material and obtained as a white solid (6.5 mg, 10% NMR yield, 6% isolated yield). **mp**: 52-55 °C. **Rf**: 0.08 (20% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.37 (dd, *J* = 8.2, 1.2 Hz, 2 H, Ph), 7.20 (t, *J* = 7.4 Hz, 2 H, Ph), 7.18 (tt, *J* = 7.3, 1.1 Hz, 1 H, *p*-Ph), 1.45 (s, 3 H, C**H_3**), 1.31 (s, 6 H, 2×C_{pin}**H_3**), 1.29 (s, 6 H, 2×C_{pin}**H_3**), 1.27 (d, *J* = 3.0 Hz, 1 H, 1×$C_{cyclopropyl}$**H_2**), 1.10 (d, *J* = 3.0 Hz, 1 H, 1×$C_{cyclopropyl}$**H_2**), –0.31 (s, 9 H, Si(C**H_3**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 146.1 (**C**q, Ar), 129.5 (2×**C**H, Ar), 127.8 (2×**C**H, Ar), 126.0 (**C**H, Ar), 83.1 (2×**C**qO), 29.7 (**C**H_3), 28.5 (**C**$q_{cyclopropyl}$), 25.3 (2×**C**$_{pin}H_3$), 25.0 (2×**C**$_{pin}H_3$), 19.7 (**C**$_{cyclopropyl}H_2$), –1.1 (Si(**C**H_3)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.1. **FTIR** (cm^{-1}) (neat): 2978, 1371, 1328, 1248, 1144, 969, 848, 768, 700.

2-Diphenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22z)



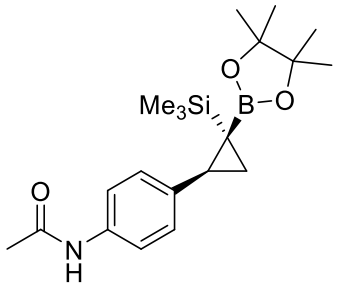
Cyclopropane **4.22z** was synthesized using general procedure G while irradiated during 64 hours, using 1,1-diphenylethylene **4.21z** (39.7 mg, 0.2 mmol) as the starting material and obtained as a white solid (15.7 mg, 19% NMR yield, 18% isolated yield). **mp**: 112-126 °C. **Rf**: 0.11 (15% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.56 (td, *J* = 7.3, 1.3 Hz, 4 H, Ph), 7.22 (t, *J* = 7.4 Hz, 2 H, Ph), 7.19 (t, *J* = 6.0 Hz, 2 H, Ph), 7.13 (tt, *J* = 7.3, 1.2 Hz, 2 H, Ph), 7.08 (tt, *J* = 7.3, 1.2 Hz, 2 H, Ph), 1.87 (d, *J* = 3.0 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.48 (d, *J* = 3.0 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.07 (s, 6 H, 2×C_{pin}**H**$_3$), 0.82 (s, 6 H, 2×C_{pin}**H**$_3$), –0.19 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 145.8 (**C**q, Ph), 145.3 (**C**q, Ph), 130.1 (2×**C**H, Ph), 129.7 (2×**C**H, Ph), 128.0 (2×**C**H, Ph), 127.9 (2×**C**H, Ph), 126.3 (**C**H, Ph), 126.1 (**C**H, Ph), 82.8 (2×**C**qO), 41.5 (**C**qPh_2), 25.3 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 18.4 (**C**$_{cyclopropyl}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.1. **FTIR** (cm^{-1}) (neat): 2923, 2853, 1455, 1372, 1345, 1305, 1263, 1244, 1140, 1090, 983, 960, 887, 836, 779, 750, 549. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{24}H_{33}{}^{11}BO_2Si$ $[M+H]^+$: 393.2416; found 393.2429.

Isopropyl 2-methyl-2-(4-(4-((1*R,2*S**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl)benzoyl)phenoxy)propanoate (4.22aa)**



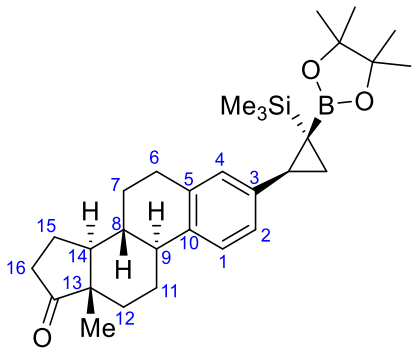
Cyclopropane **4.22aa** was synthesized using general procedure G, using vinyl-fenofibrate[205] **4.21aa** (70.5 mg, 0.2 mmol) as the starting material and obtained as a white solid (62.5 mg, 55% NMR yield, 55% isolated yield, 13:1 dr). **mp**: 78-79 °C. **Rf**: 0.10 (10% diethyl ether/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.73 (dt, *J* = 8.9, 1.9 Hz, 2 H, Ar), 7.68 (dt, *J* = 8.2, 1.5 Hz, 2 H, Ar), 7.34 (d, *J* = 8.2 Hz, 2 H, Ar), 6.86 (dt, *J* = 8.9, 1.9 Hz, 2 H, Ar), 5.11 (sept, *J* = 6.2 Hz, 1 H COOC**H**$(CH_3)_2$), 2.19 (dd, *J* = 6.8, 5.2 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.68 (s, 6 H, 2×C**H$_3$**COAr), 1.61 (dd, *J* = 4.8, 3.8 Hz, 1 H, 1×$C_{cyclopropyl}$**H$_2$**), 1.23 (d, *J* = 6.3 Hz, 6 H, COOCH(C**H$_3$**)**$_2$**), 1.11 (dd, *J* = 6.9, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H$_2$**), 0.98 (s, 6 H, 2×C_{pin}**H$_3$**), 0.94 (s, 6 H, 2×C_{pin}**H$_3$**), 0.10 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 195.2 (**C**=O), 173.2 (**C**OO*i*-Pr), 159.3 (**C**qO, Ar), 146.6 (**C**q(CO), Ar), 135.5 (**C**q(CO), Ar), 131.8 (2×**C**H, Ar), 131.1 (**C**$q_{cyclopropyl}$, Ar), 129.6 (2×**C**H, Ar), 128.2 (2×**C**H, Ar), 117.1 (2×**C**H, Ar), 82.8 (2×**C**qO), 79.3 (O**C**H$(CH_3)_2$), 69.3 (COO**C**H), 25.40 (1×**C**H_3COAr), 25.37 (1×**C**H_3COAr), 25.2 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}H_3$), 24.6 (2×**C**$_{pin}H_3$), 21.5 (COOCH(**C**H_3)**$_2$**), 13.2 (**C**$_{cyclopropyl}H_2$), 5.1 (**C**qBSi), –2.4 (Si(**C**H_3)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.3. **FTIR** (cm^{-1}) (neat): 2979, 1731, 1655, 1601, 1504, 1361, 1304, 1248, 1174, 1146, 1104, 929, 850, 764, 690, 420. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{32}H_{45}{}^{11}BO_6Si$ $[M+H]^+$: 565.3151; found 565.3165.

***N*-(4-((1*R**,2*S**)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl)phenyl)acetamide (4.22ab)**



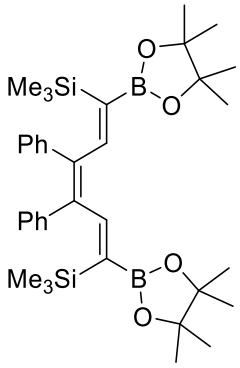
Cyclopropane **4.22ab** was synthesized using general procedure G, using *N*-(4-vinylphenyl)acetamide[206] **4.21ab** (32.2 mg, 0.2 mmol) as the starting material and obtained as a white solid (63.9 mg, 87% NMR yield, 86% isolated yield, 9:1 dr). **mp**: 104-108 °C. **Rf**: 0.26 (50% ethyl acetate/hexanes). *Major diastereomer.* **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.36 (d, *J* = 8.5 Hz, 2 H, Ar), 7.20 (d, *J* = 8.3 Hz, 2 H, Ar), 2.17 (s, 3 H, C**H$_3$**), 2.09 (dd, *J* = 6.6, 5.2 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.48 (dd, *J* = 4.8, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H$_2$**), 1.01 (dd, *J* = 7.1, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H$_2$**), 0.97 (s, 6 H, 2×C_{pin}**H$_3$**), 0.90 (s, 6 H, 2×C_{pin}**H$_3$**), 0.07 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 168.0 (**C**=O), 137.6 (**C**q-N, Ar), 135.7 (**C**q, Ar), 129.1 (2×**C**H, Ar), 119.3 (2×**C**H, Ar), 82.7 (2×**C**qO), 29.7 (CO**C**H$_3$) 24.9 (2×**C**$_{pin}$H$_3$), 24.6 (Ar**C**$_{cyclopropyl}$H), 24.5 (2×**C**$_{pin}$H$_3$), 12.7 (**C**$_{cyclopropyl}$H$_2$), –2.3 Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.1. **FTIR** (cm^{-1}) (neat): 3301, 2976, 2924, 2854, 1663, 1602, 1536, 1516, 1404, 1359, 1299, 1146, 880, 836, 758. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{20}H_{32}{}^{11}BNO_3Si$ $[M+H]^+$: 374.2217; found 374.2235.

(8*R,9*S**,13*S**,14*S**)-13-Methyl-3-((1*S**,2*S**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl)-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a] phenanthren-17(14H)-one (4.22ac)**



Cyclopropane **4.22ac** was synthesized using general procedure G, using vinyl-estrone[206] **4.21ac** (56.1 mg, 0.2 mmol) as the starting material and obtained as a white solid (82.1 mg, 96% NMR yield, 83% isolated yield, 13:1 dr). *Major diastereomer.* **mp**: 159-162 °C. **Rf**: 0.27 (20% Et_2O_2/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.14 (d, *J* = 8.0 Hz, 1 H, Ar-**H**^{1}), 7.03 (d, *J* = 7.9 Hz, 1 H, Ar-**H**^{2}), 6.96 (s, 1 H, Ar-**H**^{4}), 2.89-2.87 (m, 2 H, C^6**H$_2$**), 2.52 (dd, *J* = 19.0, 8.8 Hz, 1 H, 1×C^{16}**H**$_2$), 2.42-2.39 (m, 1 H, 1×C^{11}**H**$_2$), 2.30-2.24 (m, 1 H, C^9**H**), 2.15 (dt, *J* = 19.0, 9.1 Hz, 1 H, 1×C^{16}**H**$_2$), 2.07 (dd, *J* = 7.0, 5.4 Hz, 1 H, ArC$_{cyclopropyl}$**H**), 2.03-2.00 (m, 1 H, 1×C^{15}**H**), 1.96 (dd, *J* = 9.2, 2.6 Hz, 1 H, 1×C^7**H**), 1.68-1.60 (m, 2 H, 1×C^{12}**H**, 1×C^{15}**H**), 1.54-1.44 (m, 6 H, 1×C$_{cyclopropyl}$**H**$_2$, 1×C^7**H**$_2$, C^8**H**, 1×C^{11}**H**$_2$, 1×C^{12}**H**$_2$, 1×C^{14}**H**$_2$), 1.01-0.99 (m, 1 H, 1×C$_{cyclopropyl}$**H**$_2$), 0.97 (s, 6 H, 2×C$_{pin}$**H$_3$**), 0.92 (s, 3 H, C^{13}C**H**$_3$), 0.91 (s, 6 H, 2×C$_{pin}$**H$_3$**), 0.07 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 220.9 (C=O), 138.9 (**C**^{3}q), 137.1 (**C**^{5}q), 135.6 (**C**^{10}q), 128.8 (**C**^{1}H), 126.0 (**C**^{4}H), 124.8 (**C**^{2}H), 82.6 (2×**C**$_{pin}$O) 50.5 (**C**^{14}H), 48.0 (**C**^{13}q), 44.3 (**C**^{9}H), 38.5 (**C**^{8}H), 35.9 (**C**^{16}H$_2$), 31.6 (**C**^{12}H$_2$), 29.5 (**C**^{6}H$_2$), 26.6 (**C**^{7}H$_2$), 25.92 (**C**^{11}H$_2$), 24.89 (2×**C**$_{pin}$H$_3$), 24.83 (Ar**C**$_{cyclopropyl}$H), 24.6 (2×**C**$_{pin}$H$_3$), 21.6 (**C**^{15}H$_2$), 13.8 (C^{13}q**C**H$_3$), 12.8 (**C**$_{cyclopropyl}$H$_2$), 3.7 (**C**qBSi), –2.3 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.9. **FTIR** (cm^{-1}) (neat): 2928, 1740 (C=O), 1502, 1454, 1359, 1299, 1244, 1146, 1117, 1083, 1006, 837, 732, 579. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{30}H_{45}{}^{11}BO_3Si$ [M+H]$^+$: 493.3303; found 493.3312.

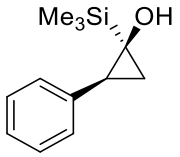
((1*Z*,3*Z*,5*Z*)-3,4-Diphenyl-1,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-triene-1,6-diyl)bis(trimethylsilane) (4.24)



Hexatriene **4.24** was synthesized using general procedure G, using phenylacetylene (20.4 mg, 0.2 mmol, 1.0 equiv) as the starting material and obtained as a white solid (31.0 mg, 48% isolated yield). **mp**: 155-157 °C. **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.34 (s, 2 H, =C**H**) 7.05-7.03 (m, 6 H, Ar), 6.98-6.95 (m, 4 H, Ar), 0.99 (s, 24 H, 8×C_{pin}**H**$_3$), 0.19 (s, 18 H, 2×Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 151.3 (2×*p*-**C**H, Ph), 142.5 (2×=**C**q), 140.7 (2×=**C**H), 131.8 2 (4×**C**H, Ph), 127.3 (4×**C**H, Ph), 126.3 (2×**C**q, Ph), 82.8 (4×**C**qO), 25.4 (8×**C**$_{pin}$H$_3$), –0.5 (2×Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.3. **FTIR** (cm^{-1}) (neat): 2976, 1572, 1443, 1371, 1230, 1245, 1142, 973, 839, 753, 698. **HRMS** (ESI, Pos) *m/z:* calcd $(C_{36}H_{54}{}^{11}B_2O_4Si_2)^+$: 629.38195, found 629.38168

7.3.5 Post-Functionalization Procedures and Characterization

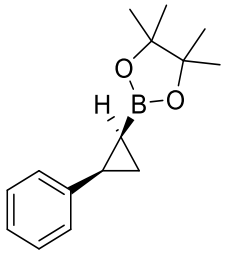
(1*S,2*R**)-2-Phenyl-1-(trimethylsilyl)cyclopropan-1-ol (4.27)**



In 25 mL round bottom flask, at 0 °C, aqueous NaOH 3 M (3.37 mL, 10.1 mmol) was added to borosilylcyclopropane **4.22a** (400 mg, 1.26 mmol) in THF (6 mL). Hydrogen peroxide solution (3.88 mL, 37.9 mmol, 30% wt) was added. The reaction mixture was allowed to warm up to room temperature and stirred during 2.5 hours. The reaction mixture was quenched with a saturated solution of sodium thiosulfate and silylcyclopropanol **4.27** was extracted from the aqueous layer

by washing with ethyl acetate (3×5mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (5% Et_2O/hexanes) to afford silylcyclopropanol **4.27** (168 mg, 64%, 11:1 dr) as a colorless oil. **Rf**: 0.26 (10% diethyl ether/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.34 (td, *J* = 7.5, 1.9 Hz, 2 H, Ph), 7.27-7.22 (m, 3 H, Ph), 2.04 (dd, *J* = 9.2, 7.0 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.22 (t, *J* = 6.4 Hz, 1 H, $C_{cyclopropyl}$**H_2**), 1.10 (dd, *J* = 9.3, 6.3 Hz, 1 H, $C_{cyclopropyl}$**H_2**), 0.13 (s, 9 H, Si(C**H_3**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 136.7 (**C**q, Ar) 129.0 (2×**C**H, Ph), 128.2 (2×**C**H, Ph), 126.2 (**C**H, Ph), 51.5 (O**C**qSiMe_3), 26.3 (Ar**C**$_{cyclopropyl}$H), 16.9 (**C**$_{cyclopropyl}H_2$), –3.7 (Si(**C**H_3)$_3$). **FTIR** (cm^{-1}) (neat): 3345, 2955, 1714, 1497, 1249, 1173, 1029, 874, 840, 756, 698. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{12}H_{18}OSi$ $[M+H]^+$: 207.1199; found 207.1196.

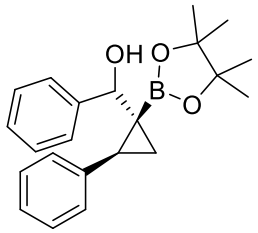
4,4,5,5-Tetramethyl-2-((1*R,2*S**)-2-phenylcyclopropyl)-1,3,2-dioxaborolane (4.28)**



The title compound was prepared according to a modified procedure reported by Suzuki.[207] In a 5 mL flame-dried microwave vial, cesium fluoride (228 mg, 1.50 mmol, 5.0 equiv) was added to borosilylcyclopropane **4.22a** (94.9 mg, 0.300 mmol, 1.0 equiv) in DMF (2 mL, 0.15 M) at room temperature. The reaction mixture was purged under nitrogen gas. The reaction vessel was sealed with a microwave cap and parafilm and the mixture was heated to 90 ºC during 20 hours. The reaction mixture was allowed to cool down to room temperature, then quenched with water. Borocyclopropane **4.28** was extracted from the aqueous layer by washing with ethyl acetate (3×5mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (2% diethyl ether/hexanes) to afford borocyclopropane **4.28** (42.5 mg, 58%, 3:1 dr,) as a colorless oil. The characterization data were identical in all respect to those reported in the literature.[120] **Rf:** 0.25 (4% diethyl ether/hexanes). *Major diastereomer.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.26-7.22 (m, 4 H, Ph), 7.17-7.14 (m, 1 H, *p*-Ph), 2.38 (ddd, *J* = 10.0, 7.7, 6.1 Hz,

1 H, Ar$C_{cyclopropyl}$**H**), 1.31 (ddd, *J* = 7.1, 6.0, 4.3 Hz, 1 H $C_{cyclopropyl}$**H**$_2$), 1.13 (ddd, *J* = 9.2, 8.1, 4.8 Hz, 1 H, $C_{cyclopropyl}$**H**$_2$), 1.03 (s, 6 H, 2×C_{pin}**H**$_3$), 0.89 (s, 6 H, 2×C_{pin}**H**$_3$), 0.46 (ddd, *J* = 10.0, 9.3, 7.2 Hz, 1 H, B$C_{cyclopropyl}$**H**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 140.8 (**C**q, Ph), 128.8 (2×**C**H, Ar), 127.7 (2×**C**H, Ar), 125.7 (**C**H, Ar), 82.9 (2×**C**qO), 24.8 (2×**C**$_{pin}$H$_3$), 24.4 (2×**C**$_{pin}$H$_3$), 21.8 (Ar**C**$_{cyclopropyl}$H), 8.9 (**C**$_{cyclopropyl}$H$_2$), 3.8 (**C**qBSi). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.2. *Minor diastereomer.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.07-7.26 (m, 5H, Ph), 2.12 (ddd, *J* = 8.0, 6.0, 5.5, 1 H, Ar$C_{cyclopropyl}$**H**), 1.26 (s, 6 H, 2×C_{pin}**H**$_3$), 1.25 (s, 6 H, 2×C_{pin}**H**$_3$), 1.17 (ddd, *J* = 8.1, 6.9, 3.7 Hz, 1 H, $C_{cyclopropyl}$**H**$_2$), 0.98-1.01 (m, 1 H, $C_{cyclopropyl}$**H**$_2$), 0.31 (ddd, *J* = 9.7, 6.8, 5.6 Hz, 1 H, B$C_{cyclopropyl}$**H**). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 143.4 (**C**q, Ph), 128.3 (2×**C**H, Ar), 125.7 (2×**C**H, Ar), 125.5 (**C**H, Ar), 83.2 (2×**C**qO), 24.4 (4×**C**$_{pin}$H$_3$), 21.9 (Ar**C**$_{cyclopropyl}$H), 15.0 (**C**$_{cyclopropyl}$H$_2$). **FTIR** (cm^{-1}) (neat): 2978, 1604, 1439, 1409, 1390, 1371, 1322, 1222, 1144, 973, 860, 772, 695, 671. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{15}H_{21}{}^{11}BO_2$ $[M+H]^+$: 245.1707; found 245.1704.

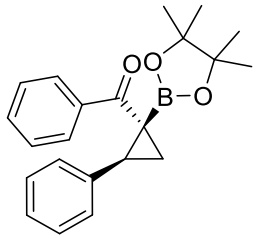
(*S*)-Phenyl((1*S,2*S**)-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) methanol (4.30)**



The title compound was prepared according to a modified procedure reported by Paquette.[208] In a flame-dried 5 mL microwave conical vial under inert atmosphere, cesium fluoride (623 mg, 4.10 mmol, 6.8 equiv) was added to borosilylcyclopropane **4.22a** (190 mg, 0.6 mmol, 1.0 equiv) in DMF (4.00 mL, 0.15 M) at room temperature. After 60 minutes, freshly distilled benzaldehyde (0.160 mL, 1.56 mmol, 2.6 equiv) was added. The reaction vessel was capped with a microwave cap, sealed with parafilm, then heated to 90 °C in an oil bath during 18 hours. The reaction mixture was allowed to cool down to room temperature, diluted with ethyl acetate and quenched with water. Borocyclopropane **4.30** was extracted from the aqueous layer by washing with ethyl acetate (3×5mL) and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (10% EtOAc /hexanes) to afford compound **4.30** (101 mg, 48%) as a yellow oil.

Rf: 0.27 (10% ethyl acetate/hexanes). *Major diastereomer.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.55 (d, *J* = 7.9 Hz, 2 H, Ph) 7.37-7.33 (m, 6 H, Ph), 7.18-7.12 (m, 1 H, Ph) 4.07 (s, 1 H, PhC**H**OH), 2.51 (dd, *J* = 7.8, 6.8 Hz, 1 H, $PhC_{cyclopropyl}\mathbf{H}$), 1.75 (dd, *J* = 6.2, 4.9 Hz, 1 H, $C_{cyclopropyl}\mathbf{H}_2$), 1.21 (dd, *J* = 8.4, 4.8 Hz, 1 H, $C_{cyclopropyl}\mathbf{H}_2$), 0.89 (s, 6 H, 2×$C_{pin}\mathbf{H_3}$), 0.65 (s, 6 H, 2×$C_{pin}\mathbf{H_3}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 145.5 (**C**q, Ph), 139.3 (**C**q, Ph), 128.9 (2×**C**H, Ph), 127.95 (2×**C**H, Ph), 127.87 (2×**C**H, Ph), 127.4 (**C**H, Ph), 127.0 (2×**C**H, Ph), 125.9 (**C**H, Ph), 83.4 (2×**C**qO), 81.0 (Ar**C**HO) 24.5 (2×$\mathbf{C}_{pin}H_3$), 24.4 (Ar$\mathbf{C}_{cyclopropyl}$H), 24.0 (2×$\mathbf{C}_{pin}H_3$), 14.3 ($\mathbf{C}_{cyclopropyl}H_2$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 31.6. *Minor diastereomer.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.49 (d, *J* = 7.3 Hz, 2 H, Ph) 7.28-7.21 (m, 8 H, Ph), 5.03 (s, 1 H, PhC**H**OH), 2.36 (dd, *J* = 8.1, 6.6 Hz, 1 H, $PhC_{cyclopropyl}\mathbf{H}$), 1.51 (dd, *J* = 6.3, 4.4 Hz, 1 H, $C_{cyclopropyl}\mathbf{H}_2$), 1.14 (dd, *J* = 8.4, 4.3 Hz, 1 H, $C_{cyclopropyl}\mathbf{H}_2$), 0.93 (s, 6 H, 2×$C_{pin}\mathbf{H_3}$), 0.77 (s, 6 H, 2×$C_{pin}\mathbf{H_3}$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 142.7 (**C**q, Ph), 139.9 (**C**q, Ph), 129.0 (2×**C**H, Ph), 128.97 (2×**C**H, Ph), 127.7 (2×**C**H, Ph), 127.5 (**C**H, Ph), 125.9 (2×**C**H, Ph), 125.8 (**C**H, Ph), 83.3 (2×**C**qO), 75.0 (Ar**C**HO) 24.6 (Ar$\mathbf{C}_{cyclopropyl}$H), 24.5 (2×$\mathbf{C}_{pin}H_3$), 24.2 (2×$\mathbf{C}_{pin}H_3$), 12.4 ($\mathbf{C}_{cyclopropyl}H_2$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 22.3. **FTIR** (cm^{-1}) (neat): 3029 br. (OH), 2978, 2926, 1694, 1496, 1451, 1410, 1318, 1288, 1137, 1025, 854, 739, 698. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{22}H_{27}{}^{11}BO_3$ $[M+Na]^+$: 373.1945; found 373.1940.

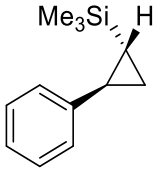
Phenyl((1*S,2*S**)-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) methanone (4.31)**



In a 10 mL flame-dried round bottom flask, a solution of dimethylsulfoxide (40.6 uL, 0.57 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL) was added to oxalyl chloride (36.7 uL, 0.43 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL) at −78 °C. After 20 minutes, borocyclopropane **4.30** (100 mg, 0.29 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) was added. After 45 minutes at −78 °C, triethylamine (200 uL, 1.4 mmol, 5.0 equiv) was added dropwise over 10 minutes. The reaction was stirred at −78 °C,

during 120 minutes, then purged during 10 minutes into a vacuum flask containing bleach. Ethyl acetate was added, then the reaction mixture was quenched with a saturated solution of ammonium chloride and borocyclopropane **4.31** was extracted from the aqueous layer by washing with ethyl acetate (3×5mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure to afford compound **4.31** (87.9 mg, 88%, >20:1 dr) as a yellow oil. **Rf**: 0.39 (10% ethyl acetate/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.98 (d, *J* = 7.2 Hz, 2 H, Ph), 7.54 (t, *J* = 7.3 Hz, 1 H, Ph), 7.46 (t, *J* = 7.7 Hz, 2 H, Ph), 7.39 (d, *J* = 7.7 Hz, 2 H, Ph), 7.29 (t, *J* = 7.5 Hz, 2 H, Ph), 7.23-7.18 (m, 1 H, Ph), 3.37 (t, *J* = 7.2, Hz, 1 H, Ph$C_{cyclopropyl}$**H**), 2.11 (dd, *J* = 6.9, 3.9 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.53 (dd, *J* = 8.5, 3.8 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 0.91 (s, 6 H, 2×C_{pin}**H**$_3$), 0.66 (s, 6 H, 2×C_{pin}**H**$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 200.2 (**C**=O), 132.0 (**C**q, Ph), 133.3 (**C**q, Ph), 129.8 (2×**C**H, Ph), 129.3 (2×**C**H, Ph), 128.5 (2×**C**H, Ph), 128.2 (2×**C**H, Ph), 127.9 (**C**H, Ph), 126.5 (**C**H, Ph), 83.7 (2×**C**qO), 28.3 (Ar**C**$_{cyclopropyl}$H), 24.3 (2×**C**$_{pin}$H$_3$), 24.2 (2×**C**$_{pin}$H$_3$), 15.5 (**C**$_{cyclopropyl}$H$_2$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 22.3. **FTIR** (cm^{-1}) (neat): 3062, 2979, 2926, 1722 (C=O), 1670, 1382, 1329, 1260, 1133, 1090, 1068, 698. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{22}H_{25}{}^{11}BO_3$ $[M+H]^+$: 349.1969; found 349.1967.

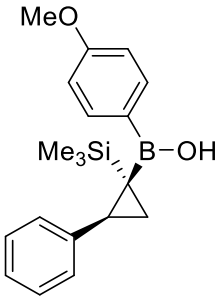
Trimethyl((1*S,2*R**)-2-phenylcyclopropyl)silane (4.32)**



In the glovebox, a flame dried 5 mL microwave vial was charged with a magnetic stir bar and potassium *t*-butoxide (279 mg, 2.49 mmol, 8.0 equiv). The vial was sealed with a microwave vial and removed from the glovebox. Borosilylcyclopropane **4.22a** (94.9 mg, 0.300 mmol, 1.0 equiv) was weighed in a separate flame dried 2 mL microwave vial, then dissolved in toluene (1.0 mL). This mixture was transferred via a cannula to the first vial and the 2 mL vial was washed with toluene (0.5 mL). The vial was sealed with parafilm and stirred at 80 °C during 18 h in an oil bath. The reaction mixture was allowed to cool down to room temperature and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (2% CH_2Cl_2/petroleum ether) to afford *trans*-silylcyclopropane **4.32** (22.8 mg, 40 %, 14:1 dr) as

colorless oil. The characterization data were identical in all respect to those reported in the literature.[209] **Rf**: 0.62 (5% dichloromethane/petroleum ether). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.27 (td, *J* = 8.0, 1.6 Hz, 2 H, Ph), 7.16 (tt, *J* = 7.4, 1.2 Hz, 3 H, *p*-Ph), 7.11 (dt, *J* = 8.4, 1.3 Hz, 2 H, Ph) 1.80 (ddd, *J* = 7.6, 6.6, 4.7, 1.2 Hz, 1 H, $ArC_{cyclopropyl}\mathbf{H}$), 0.99 (dt, *J* = 10.3, 4.4 Hz, 1 H, $C_{cyclopropyl}\mathbf{H}_2$), 0.90 (td, *J* = 11.8, 4.1 Hz, 1 H, $C_{cyclopropyl}\mathbf{H}_2$), 0.11-0.04 (m, 1 H, $SiC_{cyclopropyl}\mathbf{H}$), 0.08 (s, 9 H, $Si(C\mathbf{H_3})_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 144.6 (**C**q, Ar) 128.3 (2×**C**H, Ph), 125.6 (2×**C**H, Ph), 125.3 (**C**H, Ph), 19.7 ($Ar\mathbf{C}_{cyclopropyl}H$), 13.0 ($\mathbf{C}_{cyclopropyl}H_2$), 10.5 ($Si\mathbf{C}_{cyclopropyl}H$), –2.4 ($Si(\mathbf{C}H_3)_3$). **FTIR** ($cm^{-1}$) (neat): 2996, 2953, 2926. 2854, 1604, 1499, 1459, 1248, 1098, 980, 907, 833, 749, 695, 510.

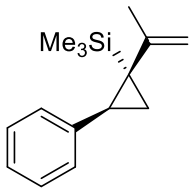
((1*S,2*R**)-1-(Hydroxy(4-methoxyphenyl)boraneyl)-2-phenylcyclopropyl)trimethylsilane (4.33)**



In a flame dried 25 mL round bottom flask, at –78 °C, *n*-butyllithium (0.64 mL, 1.60 mmol, 3.2 equiv) was added to 4-bromoanisole (290 mg, 1.55 mmol, 3.1 equiv) in THF (5.0 mL). After 60 minutes at –78 °C, a solution of borosilylcyclopropane **4.22a** (158 mg, 0.50 mmol, 1.0 equiv) in THF (5.0 mL) was added via a cannula. After 30 minutes at –78 °C, the dry ice/acetone bath was removed and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was stirred at room temperature during 60 minutes. The reaction mixture was quenched with a saturated solution of ammonium chloride and borosilylcyclopropane **4.33** was extracted from the aqueous layer by washing with ethyl acetate (3×5mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography to afford compound **4.33** (139 mg, 94%, 14:1 dr) as a white solid. **mp:** 46-50 °C. **Rf**: 0.18 (10% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.80 (dt, *J* = 8.7, 2.1 Hz, 2 H, Ar), 7.19 (tt, *J* = 7.4, 1.7 Hz, 2 H, Ph), 7.09 (tt, *J* = 7.3, 1.2 Hz, 1 H, *p*-Ph), 6.98 (dt, *J* = 8.4, 1.3 Hz, 2 H, Ph), 6.88 (dt, *J* = 8.7, 2.1 Hz, 2

H, Ar), 4.84 (s, 1 H, O**H**), 3.86 (s, 3 H, OC**H**$_3$), 2.16 (dd, *J* = 7.0, 4.3 Hz, 1 H, ArC$_{cyclopropyl}$**H**), 1.52 (t, *J* = 3.9 Hz, 1 H, C$_{cyclopropyl}$**H**$_2$), 1.49 (dd, *J* = 7.1, 3.6 Hz, 1 H, C$_{cyclopropyl}$**H**$_2$), 0.05 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 162.1 (**C**qOMe, Ar), 142.4 (**C**q, Ar), 136.8 (2×**C**H, Ar), 129.5 (**C**qBAr), 128.5 (2×**C**H, Ph), 126.2 (2×**C**H, Ph), 125.7 (**C**H, Ph), 112.9 (2×**C**H, Ar), 55.0 (O**C**H$_3$), 29.7 (**C**qBSi), 25.0 (Ar**C**$_{cyclopropyl}$H), 17.2 (**C**$_{cyclopropyl}$H$_2$), –1.9 (Si(**C**H$_3$)$_3$. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm –3.48. **FTIR** (cm^{-1}) (neat): 3345, 2955, 1714, 1497, 1249, 1173, 1029, 874, 840, 756, 698. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{19}H_{25}{}^{11}BO_2Si$ $[M+H]^+$: 325.1790; found 325.1792.

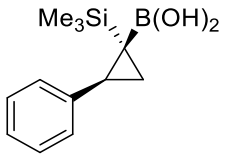
Trimethyl((1*S,2*R**)-2-phenyl-1-(prop-1-en-2-yl)cyclopropyl)silane (4.34)**



The title compound was prepared according to a modified procedure reported by Aggarwal.[210] In a 20 mL flame-dried microwave vial under inert atmosphere, *t*-butyllithium (1.7 M in pentane, 2.6 mL, 4.0 mmol, 8.0 equiv) was added dropwise to 2-bromoprop-1-ene (242 mg, 2.0 mmol, 4.0 equiv) in THF (3.0 mL) at –78 °C. After 30 minutes, borosilylcyclopropane **4.22a** (158 mg, 0.5 mmol, 1.0 equiv) was weighed in an oven and flame-dried 5 mL microwave vial, then dissolved in THF (1.5 mL). This solution was added *via* a cannula and this vial was rinsed with THF (0.5 mL). After 60 minutes at –78 °C, the mixture was warmed to –40 °C in another dry ice/acetone bath. After 60 minutes, the reaction mixture was cooled down to –78 °C again, a solution of iodine (509 mg, 2.0 mmol, 4.0 equiv) in MeOH (6.0 mL) was added *via* a cannula, then stirred at –78 °C during 30 minutes. The mixture was warmed up to 0 °C and stirred another 30 minutes. The reaction mixture was diluted with ethyl acetate and quenched with an aqueous solution of $Na_2S_2O_3$. Silylcyclopropane **4.34** was extracted from the aqueous layer by washing with ethyl acetate (3×5mL) and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (5% CH_2Cl_2/hexanes) to afford vinylsilylcyclopropane **4.34** (99.8 mg, 87%, 15:1 dr) as a colorless oil. **Rf**: 0.54 (10% CH_2Cl_2/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.22 (td, *J* = 7.1, 1.7 Hz, 2 H, Ph), 7.15 (tt, *J* = 7.3, 1.2 Hz, 1 H, *p*-Ph), 7.09 (dt, *J* = 7.2, 1.3 Hz,

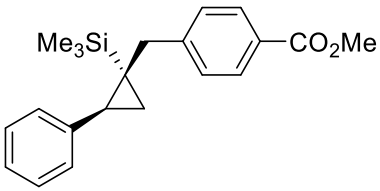
1 H, Ph), 4.84 (d, *J* = 1.4 Hz, 1 H, 1×$C_{sp2}\mathbf{H}_2$), 4.66 (d, *J* = 1.5 Hz, 1 H, 1×$C_{sp2}\mathbf{H}_2$), 2.14 (dd, *J* = 7.8, 5.8 Hz, 1 H, Ph$C_{cyclopropyl}\mathbf{H}$), 1.30-1.34 (m, 4 H, 1×$C_{cyclopropyl}\mathbf{H}_2$, $C\mathbf{H}_3$), 1.20 (dd, *J* = 7.8, 4.7 Hz, 1 H, 1×$C_{cyclopropyl}\mathbf{H}_2$), 0.07 (s, 9 H, Si($C\mathbf{H}_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 145.0 (**C**q, Ph), 139.8 (**C**H, Ph), 127.6 (2×**C**H, Ph), 127.4 (2×**C**H, Ph), 125.3 ($\mathbf{Cq}_{sp2}$), 114.4 ($\mathbf{C}_{sp2}H_2$), 28.1 ($\mathbf{Cq}_{cyclopropyl}$), 25.5 (Ar$\mathbf{C}_{cyclopropyl}$H), 23.3 ($\mathbf{C}H_3$), 16.7 ($\mathbf{C}_{cyclopropyl}H_2$), –2.5 (Si($\mathbf{C}H_3$)$_3$). **FTIR** ($cm^{-1}$) (neat): 2955, 2924, 2854, 2030, 1498, 1458, 1374, 1249, 886, 854, 836, 695. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{15}H_{22}Si$ $[M+Ag]^+$: 337.0536 m/z; found 337.0526.

((1*R,2*S**)-2-Phenyl-1-(trimethylsilyl)cyclopropyl)boronic acid (4.35)**



In a flame-dried 25 mL round bottom flask, at 0 °C boron trichloride (2.25 mL, 2.25 mmol, 1.0 M in heptane, 5.0 equiv) was added to borosilylcyclopropane **4.22a** (142.0 mg, 0.45 mmol, 1.0 equiv) in CH_2Cl_2 (1.8 mL, 0.25 M) to give a yellow solution that darkens over time. The reaction mixture was stirred at room temperature during 45 minutes. The mixture was cooled down to 0 °C, diluted with CH_2Cl_2, then MeOH was slowly added to give a lilac solution. The volatiles were removed under reduced pressure. MeOH was added again, the mixture became colorless, and the mixture was transferred to a 5 mL microwave vial. The volatiles were removed under reduced pressure to provide crude cyclopropylboronic acid **4.35** (105.2, mg, 100%). **Rf**: 0.18 (10% Et_2O/hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.15-7.05 (m, 5 H, Ph), 2.24-2.15 (m, 1 H, Ph$C_{cyclopropyl}\mathbf{H}$), 1.23 (dd, *J* = 5.1, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}\mathbf{H}_2$), 0.88 (dd, *J* = 7.3, 3.6 Hz, 1 H, 1×$C_{cyclopropyl}\mathbf{H}_2$), −0.12 (s, 9 H, Si($C\mathbf{H}_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 31.4.

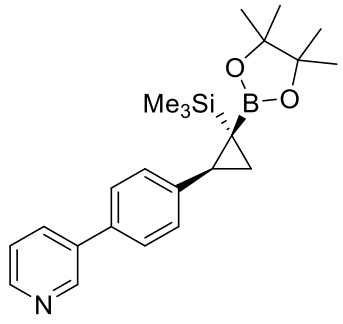
Methyl 4-(((1*S,2*S**)-2-phenyl-1-(trimethylsilyl)cyclopropyl)methyl)benzoate (4.36)**



The title compound was prepared according to a procedure reported by Merchant.[178] To the crude cyclopropylboronic acid **4.35** (105.2, mg, 1.0 equiv) were added methyl-4-((2-

tosylhydrazineylidene)methyl)benzoate (300.0 mg, 0.90 mmol, 2.0 equiv) and cesium carbonate (293.0 mg, 0.90 mmol, 2.0 equiv). The vial was purged with nitrogen gas during 10 minutes, freshly distilled 1,4-dioxane (1.80 mL, 0.25 M) was added to give an orange suspension and the reaction mixture was heated to 110 °C in a oil bath during 17 hours. The reaction mixture was allowed to cool down to room temperature, then diluted with ethyl acetate and quenched with water. Borocyclopropane **4.36** extracted from the aqueous layer by washing with ethyl acetate (3×5mL) and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (5% Et_2O/hexanes) to afford borocyclopropane **4.36** (16.7 mg, 11%, >20:1 dr) as a colorless oil. **Rf**: 0.37 (10% Et_2O/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.03 (d, *J* = 8.3 Hz, 2 H, Ar), 7.48 (d, *J* = 8.3 Hz, 2 H, Ar), 7.23 - 7.28 (m, 5 H, Ph), 3.95 (s, 3 H, $CO_2C\mathbf{H}_3$), 3.17 (d, *J* = 14.3 Hz, 1 H, 1×C$\mathbf{H}_2$), 2.50 (d, *J* = 14.3 Hz, 1 H, 1×C$\mathbf{H}_2$), 2.30 (dd, *J* = 8.2, 5.7 Hz, 1 H, PhC$_{cyclopropyl}\mathbf{H}$), 1.13 (dd, *J* = 5.6, 4.5 Hz, 1 H, 1×C$_{cyclopropyl}\mathbf{H}_2$), 0.83 (dd, *J* = 8.3, 4.4 Hz, 1 H, 1×C$_{cyclopropyl}\mathbf{H}_2$), −0.39 (s, 9 H, Si(C$\mathbf{H}_3$)$_3$).). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 167.2 (**C**O_2), 146.6 (**C**qCO_2, Ar), 140.2 (**C**q, Ph), 129.9 (2×**C**H, Ar), 129.7 (**C**H, Ar), 129.54 (2×**C**H, Ar), 129.51 (2×**C**H, Ph), 127.9 (2×**C**H, Ph), 126.2 (**C**H, Ph), 52.0 ($CO_2\mathbf{C}H_3$), 42.4 (**C**H_2), 29.0 (Ph**C**$_{cyclopropyl}$H), 15.9 (**C**q$_{cyclopropyl}$), 13.8 (**C**$_{cyclopropyl}H_2$), –1.2 (Si(**C**H_3)$_3$). **FTIR** (cm^{-1}) (neat): 2952, 2961, 2338, 1724 (C=O), 1436, 1329, 1110, 1019, 838, 762, 699. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{21}H_{26}O_2Si$ $[M+Ag]^+$: 445.0748 m/z; found 445.0768.

3-(4-((1*R,2*S**)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl)phenyl)pyridine (4.37)**



In a 5 mL flame dried microwave vial, 4-B(pin)phenyl-cyclopropane **4.22l** (98.8 mg, 0.250 mmol, 1.0 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (103 mg, 0.500 mmol, 2.0 equiv), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride•CH_2Cl_2 (20.4 mg, 0.025

mmol, 0.1 equiv) and cesium carbonate (247 mg, 0.750 mmol, 3.0 equiv) were successively weighed. The vial was purged with nitrogen gas for 5 minutes, then freshly distilled dioxane (2.27 mL, 0.10 M) and water (227 uL) were added. The reaction mixture was degassed during 5 minutes, the vial was sealed with a microwave cap and parafilm, then heated to 100 °C in an oil bath during 16 h. The reaction mixture was allowed to cool down to room temperature, then the mixture was filtered on a silica/celite (1:1 ratio) plug and rinsed with ethyl acetate. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (15% diethyl ether /hexanes) to afford cyclopropane **4.37** (92.5 mg, 94%, 14:1 dr) as a white solid.

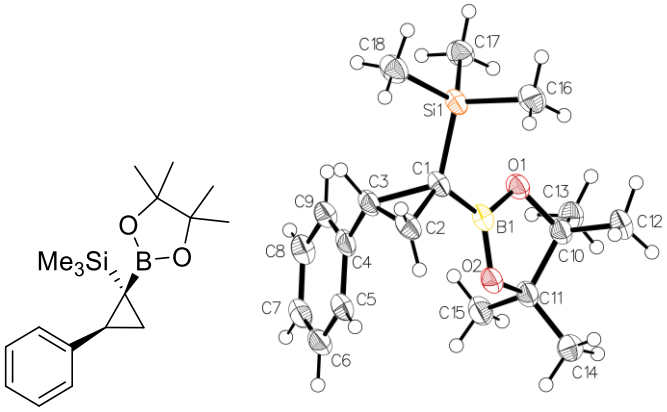
In a 5 mL flame dried microwave vial, 3-bromopyridine (39.5 mg, 0.250 mmol, 1.0 equiv), 4-bromophenyl-cyclopropane **4.22h** (221 mg, 0.500 mmol, 2.0 equiv), 1,1'-bis(diphenyl-phosphino)ferrocene palladium(II) chloride chloride•CH_2Cl_2 (20.4 mg, 0.025 mmol, 0.1 equiv) and cesium carbonate (247 mg, 0.750 mmol, 3.0 equiv) were successively weighed. The vial was purged with nitrogen gas for 5 minutes, then freshly distilled dioxane (2.27 mL, 0.1 M) and water (227 uL) were added. The reaction mixture was degassed during 5 minutes, the vial was sealed with a microwave cap and parafilm, then heated to 100 °C in an oil bath during 16 h. The reaction mixture was allowed to cool down to room temperature, then the mixture was filtered on a silica/celite (1:1 ratio) plug and rinsed with ethyl acetate. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (15% diethyl ether/hexanes) to afford cyclopropane **4.37** (86.5 mg, 88%, 9:1 dr) as a white solid.

mp. 81-83 °C. **Rf**: 0.13 (30% diethyl ether/hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.81 (d, *J* = 1.1 Hz, 1 H, pyr), 8.58 (d, *J* = 3.8 Hz, 1 H, pyr), 7.83 (dt, *J* = 7.9, 2.0 Hz, 1 H, pyr), 7.45 (dt, *J* = 8.2, 1.7 Hz, 2 H, Ar), 7.37-7.34 (m, 3 H, Ar, pyr), 2.18 (dd, *J* = 6.9, 5.3 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.57 (dd, *J* = 4.8, 3.7 Hz, 1 H, $C_{cyclopropyl}$**H**$_2$), 1.09 (dd, *J* = 7.0, 3.6 Hz, 1 H, $C_{cyclopropyl}$**H**$_2$), 0.96 (s, 6 H, 2×C_{pin}**H**$_3$), 0.91 (s, 6 H, 2×C_{pin}**H**$_3$), 0.10 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 148.2 (**C**HN, pyr), 148.1 (**C**HN, pyr), 141.8 (**C**H, pyr), 136.8 (**C**q, Ar), 135.2 (**C**q, Ar), 134.1 (**C**q, pyr), 129.3 (2×**C**H, Ar), 126.6 (2×**C**H, Ar), 123.5 (**C**H, pyr), 82.7 (2×**C**qO), 24.9 (2×**C**$_{pin}$H$_3$), 24.8 (Ar**C**$_{cyclopropyl}$H), 24.5 (2×**C**$_{pin}$H$_3$), 12.8 (**C**$_{cyclopropyl}$H$_2$), 4.2 (**C**qBSi), –2.3 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 31.8. **FTIR** (cm^{-1}) (neat): 2977, 2928, 1360, 1301, 1147, 1117, 959, 880, 843, 805, 622, 594. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{23}H_{32}{}^{11}BNO_2Si$ $[M+H]^+$: 394.2268; found 394.2280.

7.3.6 X-Ray Crystallographic Data

The data for **4.22a**,**c**,**e**,**o**,**t**,**v**,**ac**, **4.24** and **4.33**, crystallized from either diethyl ether/hexanes or diethyl ether/methanol, were collected from a shock-cooled single crystal at 100 K on a Bruker Smart APEX three-circle diffractometer with a Microfocus Source using Quazar MX Mirror Optics as monochromator and a Bruker APEX2 CCD detector. The diffractometer was equipped with an Oxford Cryostream 700 low temperature device and used Cu Kα radiation (λ = 1.54178 Å). All data were integrated with SAINT and a multi-scan absorption correction using SADABS was applied. The structure was solved by dual methods using XT and refined by full-matrix least-squares methods against F^2 by XL. Structure solution and refinement cycles were performed within the graphical user interface of OLEX2. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their Uiso values constrained to 1.5 times the Ueq of their pivot atoms for terminal sp3 carbon atoms and 1.2 times for all other carbon atoms. Disordered moieties were refined using bond lengths restraints while for the displacement parameter the refinement used a combination of restraints and constraints. This report and the CIF file were generated using FinalCif.

Borosilylcyclopropane (**4.22a**)

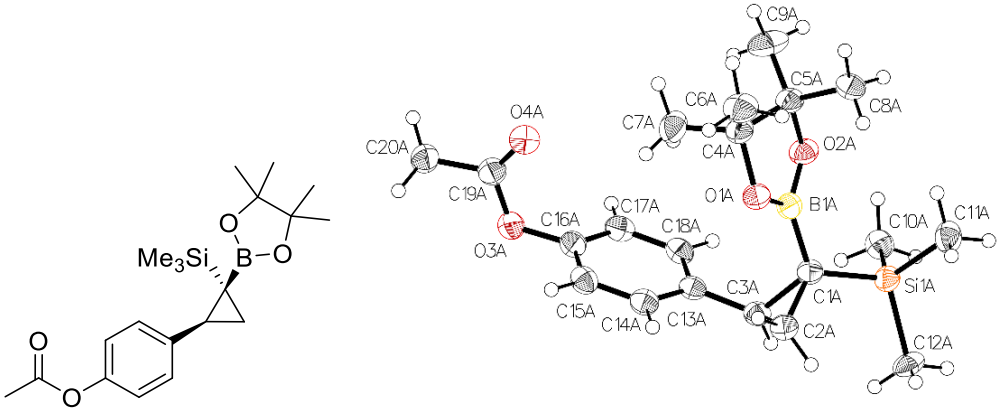


CCDC deposition number	2144797
Empirical formula	$C_{18}H_{29}BO_2Si$
Formula weight	316.31
Temperature [K]	100

Crystal system	monoclinic
Space group (number)	$P2_1/c$ (14)
a [Å]	10.2609(6)
b [Å]	6.2985(4)
c [Å]	29.0053(15)
α [Å]	90
β [Å]	95.548(3)
γ [Å]	90
Volume [Å^3]	1865.78(19)
Z	4
ρ_{calc} [g/cm^3]	1.126
μ [mm^{-1}]	1.127
F(000)	688
Crystal size [mm^3]	0.2×0.07×0.04
Crystal color	clear light colorless
Crystal shape	Block
Radiation	CuK_α (λ=1.54178 Å)
2Θ range [°]	6.12 to 140.31 (0.82 Å)
Index ranges	-12 ≤ h ≤ 12 -7 ≤ k ≤ 7 -35 ≤ l ≤ 35
Reflections collected	24345
Independent reflections	3560 R_{int} = 0.0466 R_{sigma} = 0.0303
Completeness to θ = 67.679°	100.0 %
Data / Restraints / Parameters	3560/0/206
Goodness-of-fit on F^2	1.027
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0436 wR_2 = 0.1174

Final *R* indexes	$R_1 = 0.0490$
[all data]	$wR_2 = 0.1229$
Largest peak/hole [eÅ^3]	0.41/-0.23

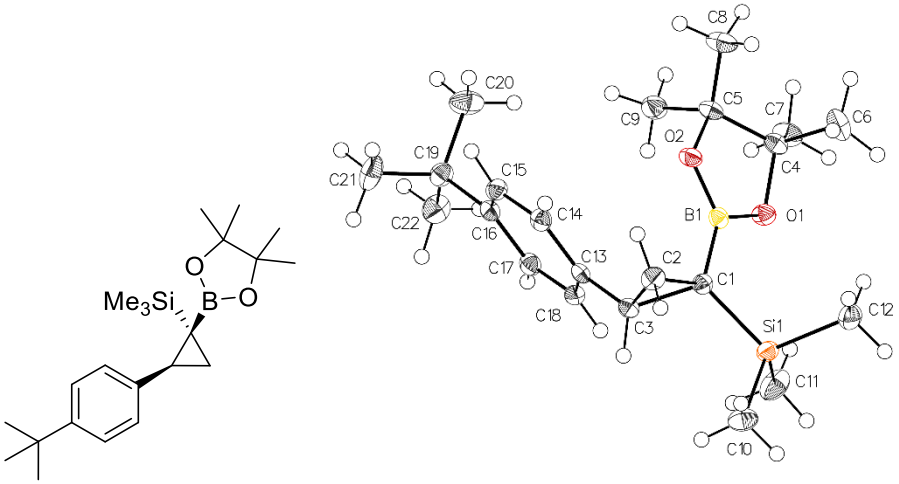
4-AcO-C_6H_4-borosilylcyclopropane (**4.22c**)



CCDC deposition number	2144799
Empirical formula	$C_{20}H_{31}BO_4Si$
Formula weight	374.35
Temperature [K]	100
Crystal system	monoclinic
Space group (number)	$P2_1/n$ (14)
a [Å]	15.1365(4)
b [Å]	8.6995(2)
c [Å]	16.9505(4)
α [°]	90
β [°]	107.339(1)
γ [°]	90
Volume [Å^3]	2130.61(9)
Z	4
ρ_{calc} [gcm^{-3}]	1.167
μ [mm^{-1}]	1.135
F(000)	808

Crystal size [mm^3]	0.15×0.17×0.19
Crystal color	colorless
Crystal shape	Plate
Radiation	CuK_α (λ=1.54178 Å)
2Θ range [°]	6.88 to 140.01 (0.82 Å)
Index ranges	$-18 \leq h \leq 17$
	$0 \leq k \leq 10$
	$0 \leq l \leq 20$
Reflections collected	4051
Independent reflections	4051
	$R_{sigma} = 0.0375$
Completeness to	100.0 %
θ = 67.679°	
Data / Restraints / Parameters	4051 / 161 / 433
Goodness-of-fit on F^2	1.050
Final R indexes	$R_1 = 0.0574$
[$I \geq 2\sigma(I)$]	w$R_2 = 0.1443$
Final R indexes	$R_1 = 0.0640$
[all data]	w$R_2 = 0.1513$
Largest peak/hole [$eÅ^{-3}$]	0.48/−0.24

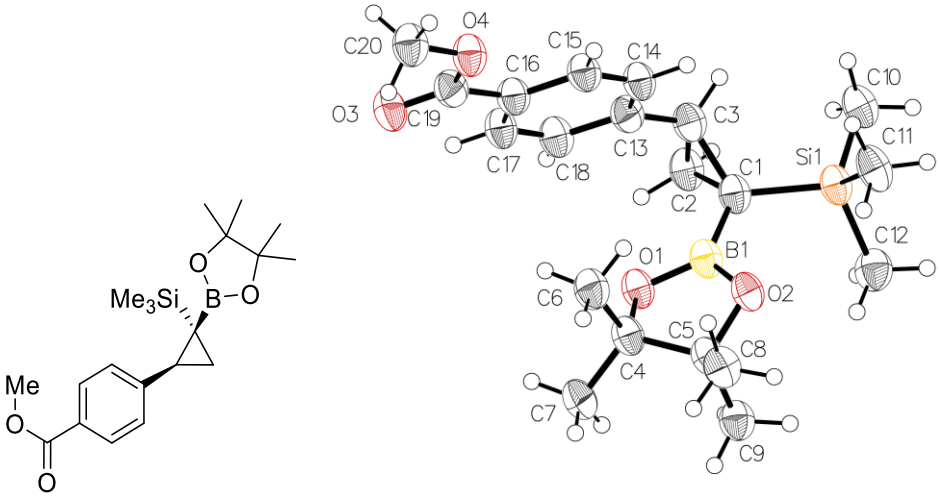
4-*t*-Bu-C_6H_4-borosilylcyclopropane (**4.22e**)



CCDC deposition number	2144800
Empirical formula	$C_{22}H_{37}BO_2Si$
Formula weight	372.41
Temperature [K]	100
Crystal system	monoclinic
Space group (number)	$P2_1/n$ (14)
a [Å]	6.3346(1)
b [Å]	24.3174(5)
c [Å]	14.9489(3)
α [°]	90
β [°]	91.598(1)
γ [°]	90
Volume [$Å^3$]	2301.85(8)
Z	4
ρ_{calc} [gcm^{-3}]	1.075
μ [mm^{-1}]	0.977
F(000)	816
Crystal size [mm^3]	0.11×0.31×0.33
Crystal color	clear light colorless
Crystal shape	Block

Radiation	Cu K_α (λ=1.54178 Å)
2Θ range [°]	6.94 to 140.29 (0.82 Å)
Index ranges	$-7 \leq h \leq 7$
	$-29 \leq k \leq 29$
	$-18 \leq l \leq 18$
Reflections collected	93524
Independent reflections	4360
	$R_{int} = 0.0318$
	$R_{sigma} = 0.0204$
Completeness to θ = 67.679°	99.6 %
Data / Restraints / Parameters	4360 / 0 / 383
Goodness-of-fit on F^2	1.065
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0371$
	$wR_2 = 0.0946$
Final R indexes [all data]	$R_1 = 0.0380$
	$wR_2 = 0.0954$
Largest peak/hole [eÅ^{-3}]	−0.26/0.39

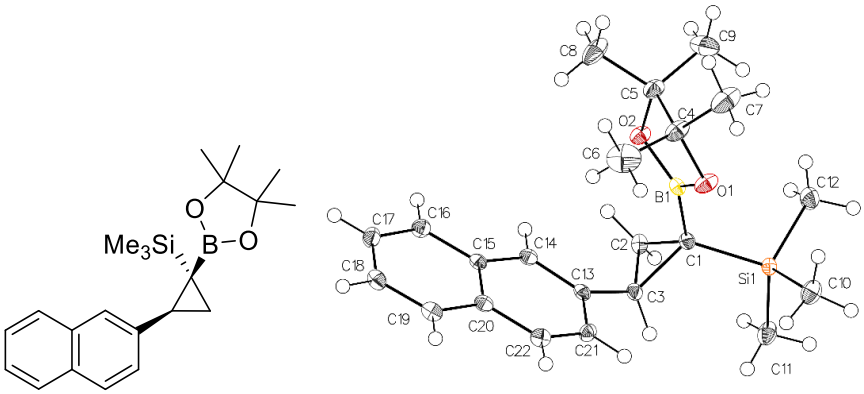
4-MeOOC-C_6H_4-borosilylcyclopropane (**4.22o**)



CCDC deposition number	2144801
Empirical formula	$C_{20}H_{31}BO_4Si$
Formula weight	374.35
Temperature [K]	100
Crystal system	triclinic
Space group (number)	$P\overline{1}$ (2)
a [Å]	6.3346(3)
b [Å]	12.9591(7)
c [Å]	13.2077(7)
α [°]	99.862(2)
β [°]	98.253(2)
γ [°]	94.942(3)
Volume [Å^3]	1050.31(9)
Z	2
ρ_{calc} [gcm^{-3}]	1.184
μ [mm^{-1}]	1.151
F(000)	404
Crystal size [mm^3]	0.22×0.13×0.09
Crystal color	clear light colorless
Crystal shape	Fragment
Radiation	Cu K_α (λ=1.54178 Å)
2Θ range [°]	6.88 to 140.21 (0.82 Å)
Index ranges	-7 ≤ h ≤ 7 -15 ≤ k ≤ 15 -16 ≤ l ≤ 16
Reflections collected	20118
Independent reflections	3940 R_{int} = 0.0565 R_{sigma} = 0.0405
Completeness to Θ = 67.679°	99.4 %

Data / Restraints / Parameters	3940/0/243
Goodness-of-fit on F^2	1.061
Final R indexes	$R_1 = 0.0512$
[$I \geq 2\sigma(I)$]	w$R_2 = 0.1363$
Final R indexes	$R_1 = 0.0560$
[all data]	w$R_2 = 0.1414$
Largest peak/hole [eÅ^{-3}]	0.28/-0.26

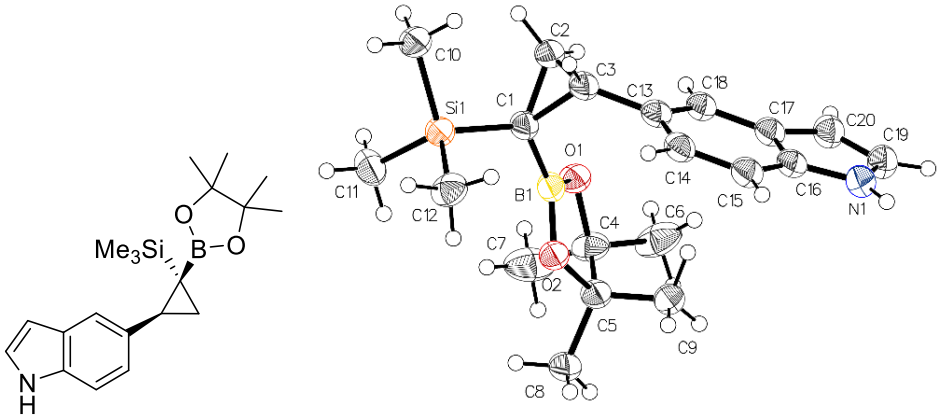
2-Naphthalenyl-borosilylcyclopropane (**4.22t**)



CCDC deposition number	2144802
Empirical formula	$C_{22}H_{31}BO_2Si$
Formula weight	366.37
Temperature [K]	100
Crystal system	monoclinic
Space group (number)	$P2_1/n$ (14)
a [Å]	9.5026(3)
b [Å]	11.8038(4)
c [Å]	19.0668(6)
α [°]	90
β [°]	102.6170(10)
γ [°]	90
Volume [Å^3]	2087.02(12)

Z	4
ρ_{calc} [gcm^{-3}]	1.166
μ [mm^{-1}]	1.077
F(000)	792
Crystal size [mm^3]	0.19×0.25×0.33
Crystal color	clear light colorless
Crystal shape	chunk
Radiation	CuK_α (λ=1.54178 Å)
2Θ range [°]	8.87 to 143.99 (0.81 Å)
Index ranges	-11 ≤ h ≤ 11
	-14 ≤ k ≤ 14
	–23 ≤ l ≤ 23
Reflections collected	83417
Independent reflections	4108
	R_{int} = 0.0425
	R_{sigma} = 0.0132
Completeness to θ = 67.679°	100.0 %
Data / Restraints / Parameters	4108 / 0 / 242
Goodness-of-fit on F^2	1.047
Final R indexes [I≥2σ(I)]	R_1 = 0.0369
	wR_2 = 0.1025
Final R indexes [all data]	R_1 = 0.0377
	wR_2 = 0.1033
Largest peak/hole [eÅ^{-3}]	−0.31/0.45

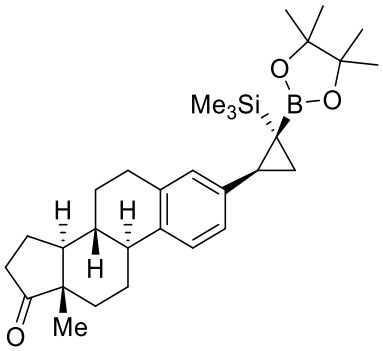
5-Indole-borosilylcyclopropane (**4.22v**)

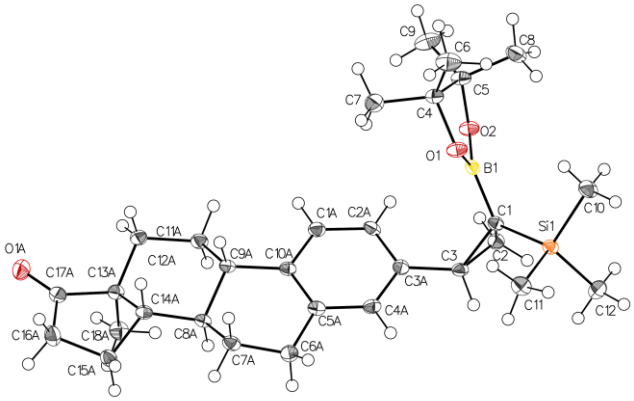


CCDC deposition number	2144803
Empirical formula	$C_{20}H_{30}BNO_2Si$
Formula weight	355.35
Temperature [K]	100
Crystal system	monoclinic
Space group (number)	$P2_1/c$ (14)
a [Å]	12.3038(13)
b [Å]	12.3367(12)
c [Å]	14.1364(12)
α [°]	90
β [°]	106.974(5)
γ [°]	90
Volume [Å^3]	2052.3(3)
Z	4
ρ_{calc} [gcm^{-3}]	1.150
μ [mm^{-1}]	1.093
F(000)	768
Crystal size [mm^3]	0.05×0.22×0.45
Crystal color	clear light colorless
Crystal shape	Plate
Radiation	Cu K_α (λ=1.54178 Å)

2Θ range [°]	7.51 to 140.46 (0.82 Å)
Index ranges	$-14 \leq h \leq 14$
	$-13 \leq k \leq 14$
	$-17 \leq l \leq 17$
Reflections collected	22611
Independent reflections	3880
	$R_{int} = 0.0635$
	$R_{sigma} = 0.0406$
Completeness to	99.9 %
θ = 67.679°	
Data / Restraints / Parameters	3880 / 0 / 233
Goodness-of-fit on F^2	1.033
Final R indexes	$R_1 = 0.0455$
[$I \geq 2\sigma(I)$]	w$R_2 = 0.1279$
Final R indexes	$R_1 = 0.0549$
[all data]	w$R_2 = 0.1365$
Largest peak/hole [eÅ^{-3}]	0.39/−0.26

Estrone-borosilylcyclopropane (**4.22ac**)



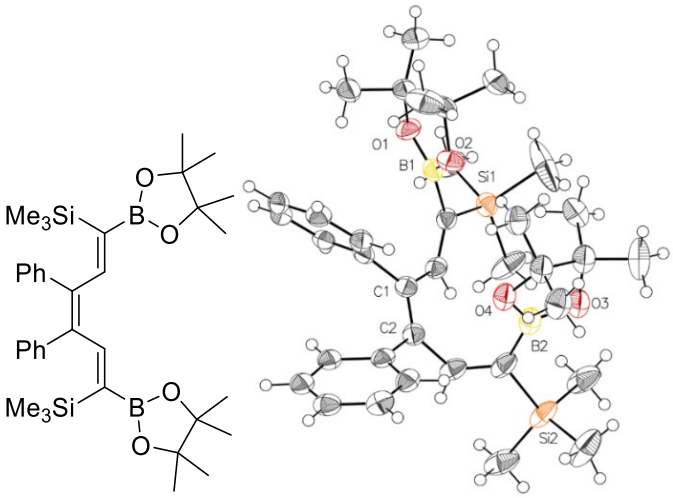


CCDC deposition number	2144798
Empirical formula	$C_{30}H_{45}BO_3Si$
Formula weight	492.56

Temperature [K]	100
Crystal system	monoclinic
Space group (number)	$P2_1$ (4)
a [Å]	6.78780(10)
b [Å]	25.7220(4)
c [Å]	8.05800(10)
α [°]	90
β [°]	98.0020(10)
γ [°]	90
Volume [Å^3]	1393.19(3)
Z	2
ρ_{calc} [gcm^{-3}]	1.174
μ [mm^{-1}]	0.955
F(000)	536
Crystal size [mm^3]	0.21×0.31×0.44
Crystal color	clear light colorless
Crystal shape	Fragment
Radiation	Cu K_α (λ=1.54178 Å)
2Θ range [°]	6.87 to 140.19 (0.82 Å)
Index ranges	-7 ≤ h ≤ 8
	-31 ≤ k ≤ 31
	-9 ≤ l ≤ 9
Reflections collected	19175
Independent reflections	5186
	R_{int} = 0.0225
	R_{sigma} = 0.0213
Completeness to θ = 67.679°	99.8 %
Data / Restraints / Parameters	5186 / 1 / 325
Goodness-of-fit on F^2	1.067

Final *R* indexes	$R_1 = 0.0272$
[$I \geq 2\sigma(I)$]	w$R_2 = 0.0721$
Final *R* indexes	$R_1 = 0.0273$
[all data]	w$R_2 = 0.0722$
Largest peak/hole [eÅ^{-3}]	0.32/−0.22
Flack X parameter	0.05(2)

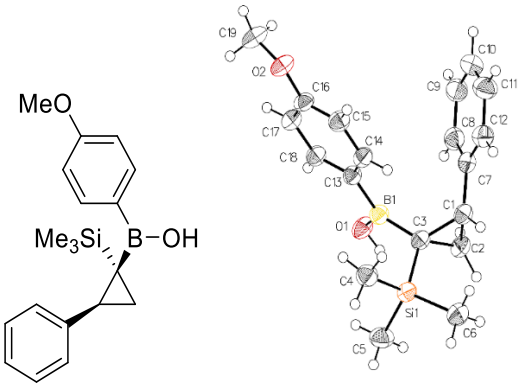
Hexatriene (**4.24**)



Empirical formula	$C_{18}H_{27}BO_2Si$
Formula weight	314.29
Temperature [K]	100
Crystal system	orthorhombic
Space group (number)	$P2_12_12_1$ (19)
a [Å]	10.0550(4)
b [Å]	11.9035(5)
c [Å]	32.1151(13)
α [°]	90
β [°]	90
γ [°]	90
Volume [Å^3]	3843.8(3)

Z	8
ρ_{calc} [gcm^{-3}]	1.086
μ [mm^{-1}]	1.094
F(000)	1360
Crystal size [mm^3]	0.19×0.32×0.34
Crystal colour	clear light colourless
Crystal shape	Block
Radiation	Cu K_α (λ=1.54178 Å)
2Θ range [°]	5.50 to 140.62 (0.82 Å)
Index ranges	-12 ≤ h ≤ 12
	-14 ≤ k ≤ 14
	-38 ≤ l ≤ 39
Reflections collected	43823
Independent reflections	7311
	R_{int} = 0.0683
	R_{sigma} = 0.0456
Completeness to θ = 67.679°	100.0 %
Data / Restraints / Parameters	7311 / 306 / 514
Goodness-of-fit on F^2	1.047
Final R indexes [I≥2σ(I)]	R_1 = 0.0521
	wR_2 = 0.1380
Final R indexes [all data]	R_1 = 0.0546
	wR_2 = 0.1401
Largest peak/hole [eÅ^{-3}]	0.34/−0.21
Flack X parameter	0.04(4)

Cyclopropylborinic acid (**4.33**)



CCDC deposition number	2144804
Empirical formula	$C_{19}H_{25}BO_2Si$
Formula weight	324.29
Temperature [K]	100
Crystal system	triclinic
Space group (number)	$P\bar{1}$ (2)
a [Å]	8.4992(5)
b [Å]	9.0820(6)
c [Å]	12.6176(7)
α [°]	72.535(3)
β [°]	87.323(3)
γ [°]	84.001(4)
Volume [Å^3]	923.84(10)
Z	2
ρ_{calc} [gcm^{-3}]	1.166
μ [mm^{-1}]	1.157
F(000)	348
Crystal size [mm^3]	0.17×0.25×0.33
Crystal color	clear light colorless
Crystal shape	Block
Radiation	Cu K_α (λ=1.54178 Å)

2Θ range [°]	7.35 to 140.23 (0.82 Å)
Index ranges	$-10 \leq h \leq 10$
	$-9 \leq k \leq 10$
	$-15 \leq l \leq 15$
Reflections collected	16133
Independent reflections	3476
	$R_{int} = 0.0433$
	$R_{sigma} = 0.0314$
Completeness to	99.8 %
θ = 67.679°	
Data / Restraints / Parameters	3476 / 0 / 216
Goodness-of-fit on F^2	1.059
Final R indexes	$R_1 = 0.0575$
[$I \geq 2\sigma(I)$]	w$R_2 = 0.1665$
Final R indexes	$R_1 = 0.0634$
[all data]	w$R_2 = 0.1788$
Largest peak/hole [eÅ^{-3}]	0.57/−0.37

7.4 Experimental Section of Chapter 5

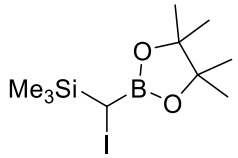
7.4.1 General procedure H: Microwave-Assisted Borotrimethylsilylcyclopropanation

In a flame-dried 5 mL microwave vial, styrene (0.09 mmol, 1.0 equiv) and (TMS)I_2CB(pin) **4.20a** (105 mg, 0.22 mmol, 2.5 equiv) were successively weighed. The vial was purged under nitrogen during 5 minutes. Acetonitrile (900 µL, 0.10 M), then DIPEA (63 µL, 0.36 mmol, 4.0 equiv) were successively added to give a yellow solution. The septum was rapidly changed for a microwave cap, then the reaction mixture was submitted to 100 °C under microwave irradiation during 3 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL), triphenylmethane (11.0 mg, 0.045 mmol, 0.5 equiv) was added as the internal standard, the mixture was filtered over a pad of silica and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography

using dichloromethane and hexanes to afford borosilylmethyl iodide **5.1** and cyclopropanes **4.22e,z** and **5.3.**

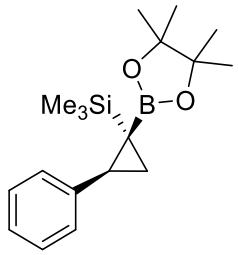
7.4.2 Characterization Data

(Iodo(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)trimethylsilane (5.1)



Borosilylmethyl iodide **5.1** was synthesized using general procedure H, with no styrene, using (TMS)I_2CB(pin) **4.20a** (105 mg, 0.22 mmol, 1.0 equiv) and DIPEA (63 µL, 0.36 mmol, 1.6 equiv). Borosilylmethyl iodide **5.1** was obtained as a colorless liquid (37.6 mg, 49% isolated yield). **Rf**: 0.63 (70% CH_2Cl_2/hexanes).**^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 1.87 (s, 1 H, C**H**I), 1.273 (s, 6 H, 2×Cpin**H$_3$**), 1.271 (s, 6 H, 2×Cpin**H$_3$**), 0.22 (s, 9 H, Si(C**H$_3$**)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 83.9 (2×**C**qO), 24.57 (2×**C**pinH_3), 24.51 (2×**C**pinH_3), –1.1 (Si(**C**H_3)$_3$), -12.3 (**C**HBSi). **^{11}B NMR** (160 MHz, $CDCl_3$) δ ppm 32.4. **FTIR** (cm^{-1}) (neat): 2978, 1467, 1370, 1318, 1270, 1248, 1214, 1142, 1063, 969, 900, 837, 754, 728, 694, 674, 616, 578, 430. Compound **5.1** was unstable under various ionization techniques and HRMS could not be obtained.

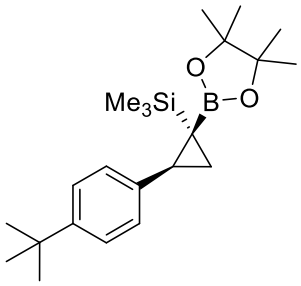
Trimethyl((1*S,2*R**)-2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl) silane (4.22a)**



Cyclopropane **4.22a** was synthesized using general procedure H, using styrene **4.21a** (11.5 mg, 0.10 mmol) as the starting material and obtained as a white solid (28.3 mg, 75% NMR yield, 69% isolated yield, 7:1 dr). **mp**: 47-49 °C. **Rf**: 0.18 (20% CH_2Cl_2/hexanes). *Major diastereomer.* **^{1}H NMR** (700 Hz, $CDCl_3$) δ ppm 7.26-7.21 (m, 4 H, Ph), 7.12 (t, *J* = 7.2 Hz, 1 H, *p*-Ph), 2.14 (dd, *J* = 6.8, 5.4 Hz, 1 H, Ar$C_{cyclopropyl}$**H**), 1.53 (dd, *J* = 4.7, 3.7 Hz, 1 H, 1×$C_{cyclopropyl}$**H$_2$**), 1.02 (dd, *J* = 7.0, 3.5 Hz, 1 H, 1×$C_{cyclopropyl}$**H$_2$**), 0.95 (s, 6 H, 2×C_{pin}**H$_3$**), 0.88 (s, 6 H, 2×C_{pin}**H$_3$**), 0.08 (s, 9 H,

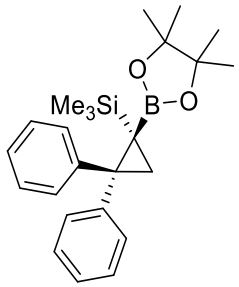
Si(C**H**$_3$)$_3$). **^{13}C NMR** (176 MHz, $CDCl_3$) δ ppm 141.4 (**C**q, Ph), 128.6 (2×**C**H, Ph), 127.8 (2×**C**H, Ph), 125.7 (**C**H, Ph), 82.6 (2×**C**qO), 25.1 (Ar**C**$_{cyclopropyl}$H), 24.9 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 12.5 (**C**$_{cyclopropyl}$H$_2$), 3.7 (**C**qBSi), –2.3 (Si(**C**H$_3$)$_3$). **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.4. **FTIR** (cm^{-1}) (neat): 2977, 2898, 1603, 1496, 1360, 1331, 1302, 1247, 1145, 1118, 959, 880, 849, 838, 759, 696. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{18}H_{30}{}^{11}BO_2Si$ $[M+H]^+$: 317.2102; found 317.2117.

((1*S,2*R**)-2-(4-(*tert*-Butyl)phenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22e)**



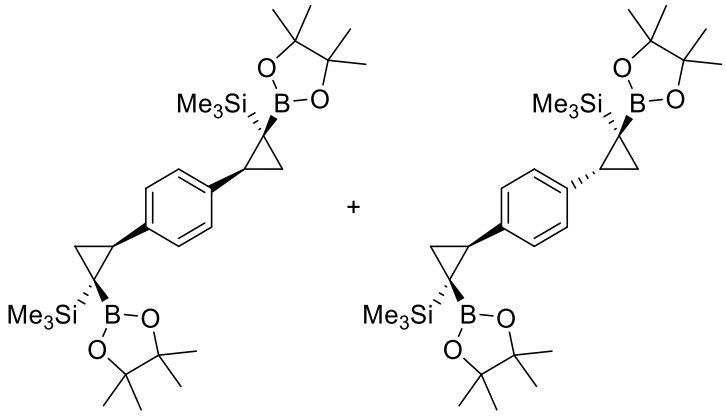
Cyclopropane **4.22e** was synthesized using general procedure H, using 4-*t*-butylstyrene **4.21e** (14.4 mg, 0.09 mmol) as the starting material and obtained as a white solid (23.8 mg, 78% NMR yield, 71% isolated yield, 10:1 dr). **mp**: 61-79 °C. **Rf**: 0.08 (10% CH_2Cl_2/hexanes). *Major diastereomer*. **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.26 (dt, *J* = 8.4, 2.0 Hz, 2 H, Ar), 7.18 (dt, *J* = 8.3, 2.1 Hz, 2 H, Ar), 2.13 (dd, *J* = 6.9, 5.1 Hz, 1 H, ArC$_{cyclopropyl}$**H**), 1.52 (dd, *J* = 4.9, 3.6 Hz, 1 H, 1×C$_{cyclopropyl}$**H**$_2$), 1.29 (s, 9 H, 3×C$_{t\text{-}Bu}$**H**$_3$), 1.00 (dd, *J* = 7.0, 3.6 Hz, 1 H, 1×C$_{cyclopropyl}$**H**$_2$), 0.94 (s, 6 H, 2×C$_{pin}$**H**$_3$), 0.86 (s, 6 H, 2×C$_{pin}$**H**$_3$), 0.08 (s, 9H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 148.5 (**C**q, Ar), 138.3 (**C**q, Ar), 128.2 (2×**C**H, Ar), 124.7 (2×**C**H, Ar), 82.6 (2×**C**qO), 34.3 (**C**q(CH$_3$)$_3$), 31.4 (3×**C**$_{t\text{-}Bu}$H$_3$), 24.8 (2×**C**$_{pin}$H$_3$), 24.5 (Ar**C**$_{cyclopropyl}$H), 24.4 (2×**C**$_{pin}$H$_3$), 12.3 (**C**$_{cyclopropyl}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 33.1. **FTIR** (cm^{-1}) (neat): 2960, 1359, 1300, 1245, 1146, 1117, 836, 759. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{22}H_{37}{}^{11}BO_2Si$ $[M+H]^+$: 373.2728; found 373.2739.

2-Diphenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)trimethylsilane (4.22z)



Cyclopropane **4.22z** was synthesized using general procedure H while irradiated during 8 hours, using 1,1-diphenylethylene **4.21z** (16.2 mg, 0.09 mmol) as the starting material and obtained as a white solid (26.7 mg, 55% NMR yield, 62% isolated yield). **mp**: 112-126 °C. **Rf**: 0.11 (15% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.56 (td, *J* = 7.3, 1.3 Hz, 4 H, Ph), 7.22 (t, *J* = 7.4 Hz, 2 H, Ph), 7.19 (t, *J* = 6.0 Hz, 2 H, Ph), 7.13 (tt, *J* = 7.3, 1.2 Hz, 2 H, Ph), 7.08 (tt, *J* = 7.3, 1.2 Hz, 2 H, Ph), 1.87 (d, *J* = 3.0 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.48 (d, *J* = 3.0 Hz, 1 H, 1×$C_{cyclopropyl}$**H**$_2$), 1.07 (s, 6 H, 2×C_{pin}**H**$_3$), 0.82 (s, 6 H, 2×C_{pin}**H**$_3$), –0.19 (s, 9 H, Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 145.8 (**C**q, Ph), 145.3 (**C**q, Ph), 130.1 (2×**C**H, Ph), 129.7 (2×**C**H, Ph), 128.0 (2×**C**H, Ph), 127.9 (2×**C**H, Ph), 126.3 (**C**H, Ph), 126.1 (**C**H, Ph), 82.8 (2×**C**qO), 41.5 (**C**qPh_2), 25.3 (2×**C**$_{pin}$H$_3$), 24.5 (2×**C**$_{pin}$H$_3$), 18.4 (**C**$_{cyclopropyl}$H$_2$), –2.3 (Si(**C**H$_3$)$_3$). Carbon attached to the boron was not observed due to quadrupolar relaxation. **^{11}B NMR** (128 MHz, $CDCl_3$) δ ppm 32.1. **FTIR** (cm^{-1}) (neat): 2923, 2853, 1455, 1372, 1345, 1305, 1263, 1244, 1140, 1090, 983, 960, 887, 836, 779, 750, 549. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{24}H_{33}{}^{11}BO_2Si$ $[M+H]^+$: 393.2416; found 393.2429.

1,4-Bis((1*S,2*R**)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trimethylsilyl)cyclopropyl)benzene (5.3)**



Dicyclopropane **5.3** was synthesized using general procedure H, using divinylbenzene[185] (13.0 mg, 0.10 mmol, 1.0 equiv) as the starting material, (TMS)I_2CB(pin) **4.20a** (233.0 mg, 0.50 mmol, 5.0 equiv) and DIPEA (139 μL, 0.8 mmol, 8.0 equiv). Dicyclopropane **5.3** was obtained as a white solid (34.3 mg, 57% NMR yield, 64% isolated yield, 5:1 dr). *Major diastereomer.* **mp**: 112-116 °C. **Rf**: 0.44 (70% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.07 (s, 4 H, Ar), 2.03 (dd, *J* = 7.1, 5.1 Hz, 2 H, 2×Ar$C_{cyclopropyl}$**H**), 1.45 (dd, *J* = 5.0, 3.6 Hz, 2 H, 2×$C_{cyclopropyl}$**H**$_2$), 0.98 (s, 12 H, 4×C_{pin}**H**$_3$), 0.97 (d, *J* = 3.5 Hz, 2 H, 2×$C_{cyclopropyl}$**H**$_2$), 0.92 (s, 12 H, 4×C_{pin}**H**$_3$), 0.06 (s, 18 H, 2×Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 138.8 (2×**C**q, Ph), 127.7 (4×**C**H, Ph), 82.6 (4×**C**qO), 24.9 (4×**C**$_{pin}$H$_3$), 24.8 (2×Ar**C**$_{cyclopropyl}$H), 24.5 (4×**C**$_{pin}$H$_3$), 12.8 (2×**C**$_{cyclopropyl}$H$_2$), 3.6 (2×**C**qBSi), –2.3 (2×Si(**C**H$_3$)$_3$). **^{11}B NMR** (160 MHz, $CDCl_3$) δ ppm 35.1. **FTIR** (cm^{-1}) (neat): 2978, 1516, 1453, 1361, 1300, 1245, 1147, 1118, 1080, 960, 941, 881, 840, 756, 688, 615, 579, 546, 424. **HRMS** (ESI, Pos) *m/z:* calcd for $C_{30}H_{52}{}^{11}B_2O_4Si_2$ $[M+NH_4]^+$: 572.3940; found 572.3953. *Minor diastereomer.* **Rf**: 0.53 (70% CH_2Cl_2/hexanes). **^{1}H NMR** (500 Hz, $CDCl_3$) δ ppm 7.13-7.11 (m, 4 H, Ar), 2.41 (dd, *J* = 7.2, 5.4 Hz, 2 H, 2×Ar$C_{cyclopropyl}$**H**), 2.08 (ddd, *J* = 8.4, 7.3, 4.8 Hz, 2 H, 2×$C_{cyclopropyl}$**H**$_2$), 1.25 (s, 12 H, 4×C_{pin}**H**$_3$), 1.24 (s, 12 H, 4×C_{pin}**H**$_3$), 1.13 (ddd, *J* = 5.2, 2.6, 2.3 Hz, 2 H, 2×$C_{cyclopropyl}$**H**$_2$), –0.25 (s, 18 H, 2×Si(C**H**$_3$)$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 129.6 (2×**C**q, Ph), 127.9 (4×**C**H, Ph), 82.6 (4×**C**qO), 25.0 (2×Ar**C**$_{cyclopropyl}$H), 24.7 (4×**C**$_{pin}$H$_3$), 24.6 (4×**C**$_{pin}$H$_3$), 12.3 (2×**C**$_{cyclopropyl}$H$_2$), 3.9 (2×**C**qBSi), –0.7 (2×Si(**C**H$_3$)$_3$).

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